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#14

Lilly

Eli Lilly and Company
Patent Division

Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

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VIA UPS

May 11, 1999

Ms. Karen Tyson
Assistant Commissioner of Patents
United States Patent & Trademark Office
Box Patent Extension
Washington, DC 20231

RE: U.S. Patent Number 4,418,068
Issued: 11-29-83
Our Reference: X-5526A

Dear Ms. Tyson:

Per our conversation of today's date, enclosed please find a complete copy of the Request for Extension of Patent Term which we filed with the USPTO on January 20, 1998. I have also included a copy of the post-card which has been stamped by your office as having been received.

If you need anything further, please do not hesitate to contact me.

Very truly yours,

Linda S. Earl

Linda S. Earl
Administrative Assistant to James J. Sales

:lse
Enclosures

PATENT

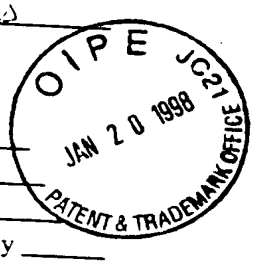
Dkt. No. X-552A Atty GJS

RECEIVED BY THE UNITED STATES
PATENT AND TRADEMARK OFFICE

~~Serial~~ Patent No. 4,418,068 OR Interference No. _____

~~Filed~~ Issued: 11-29-83 Parties: _____

Applicants: Jones _____



Response _____	Amendment/Response _____
IDS/1449 _____	Assignment/Cover Sheet _____
Notice of Appeal _____	Issue Fee _____
Letter Trans./Brief _____	Express Abandonment _____
Affirm 821/Diskette _____	Fee Authorization _____
Trans./Decl. Power Atty _____	Communication _____

Other Papers:

Request for Extension + Letter Transmitting Request for Extension

~~Certificate of Mailing~~

Express Mail EM533399863US

"Express Mail" mailing label number EM538329863US
Date of Deposit January 20, 1998
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231..

Gilbert T. Voy
Printed Name

Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,418,068

Patentee : Charles D. Jones

Assignee : Eli Lilly and Company

Issue Date : November 29, 1983

Attn: Box Patent Ext.

Attorney Docket: X-5526A

LETTER OF TRANSMITTAL OF REQUEST FOR EXTENSION OF PATENT TERM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is a request for extension of term of U.S. Patent No. 4,418,068 and a duplicate thereof, certified as such.

Please charge the filing fee of $1,120 to deposit account No. 05-0840 in the name of Eli Lilly and Company. An original and two copies of this paper are enclosed. The Assistant Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to account No. 05-0840.

The request transmitted herewith has been executed by the undersigned agent of the owner of record of the subject patent. Therefore, the present request is complete and entitled to a filing date of January 20, 1998, as indicated by the Certificate of Mailing by "Express Mail".

ELI LILLY AND COMPANY

By: _____
James J. Sales
Associate General Patent Counsel
Registration No. 33,773
Phone: 317-276-3474

Eli Lilly and Company
Patent Division/JJS
Lilly Corporate Center
Indianapolis, Indiana 46285

January 20, 1998

EM538329863US

"Express Mail" mailing label number EM538329863US

Date of Deposit January 20, 1998

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231..

Gilbert T. Voy
Printed Name

Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,418,068

Patentee : Charles D. Jones Attn: Box Patent Ext.

Assignee : Eli Lilly and Company

Issue Date : November 29, 1983

REQUEST FOR EXTENSION OF

PATENT TERM UNDER 35 U.S.C. 156

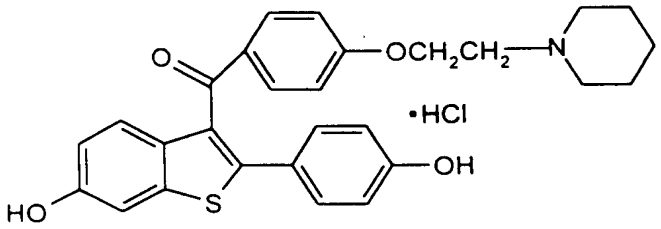
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. 156, Eli Lilly and Company, owner of the above-identified patent by an Assignment recorded on August 5, 1983, in Reel 4152, Frame 627, hereby requests an extension of the patent term of U.S. Patent No. 4,418,068. The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 *et seq.* and follows the numerical format set forth in 37 C.F.R. 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is raloxifene hydrochloride which has the chemical name [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]{4 [2-(1-piperidinyl)ethoxy]phenyl}methanone hydrochloride and has the following structure:



Raloxifene hydrochloride is the active ingredient in the product Evista® as may be seen from attached Exhibit A, which is the Product Information sheet for this product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 301 *et seq.* Section 505 provides for the submission and approval of new drug applications (NDAs) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Raloxifene hydrochloride was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on December 9, 1997.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial

marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

As stated in Sections 1, 2, and 3 above, the active ingredient in the product Evista® is raloxifene hydrochloride. Raloxifene hydrochloride had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act until December 9, 1997.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on December 9, 1997 and the last day within the sixty day period permitted for submission of a request for extension of a patent is February 7, 1998. Since February 7, 1998 is a Saturday, the application may be timely filed on February 9, 1998, the next succeeding business day in accordance with 35 U.S.C. 21. As evident from the Certificate of Mailing by "Express Mail" pursuant to 37 C.F.R. 1.10, this application is timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No.: 4,418,068
Inventor: Charles D. Jones
Issued: November 29, 1983
Expires: April 3, 2001

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A copy of the patent is attached as Exhibit B.

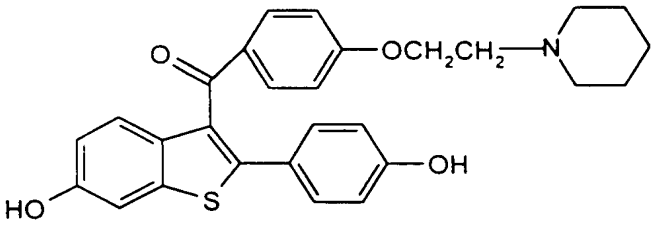
(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

A copy of the Certificate of Correction is attached as Exhibit C.

Copies of the receipts of maintenance fee payments are attached as Exhibit D.

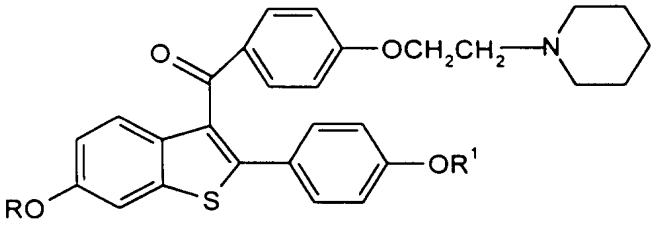
(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims the approved product, which is [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]{4-[2-(1-piperidinyl)ethoxy]phenyl}methanone hydrochloride. Claim 1 of the patent claims a "compound of the formula



a physiological acceptable ester or ether thereof, or a physiologically acceptable acid addition salt thereof." As this is the structure of raloxifene, claim 1 reads upon the approved product.

Claim 2 of the patent claims a "compound of claim 1 of the formula



wherein R and R^1 independently are hydrogen, $-COR^2$ or R^3;
R^2 is hydrogen, C_1-C_{14} alkyl, C_1-C_3 chloroalkyl, C_1-C_3 fluoroalkyl, C_5-C_7 cycloalkyl, C_1-C_4 alkoxy, phenyl, or phenyl mono- or disubsubstituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl;
R^3 is C_1-C_4 alkyl, C_5-C_7 cycloalkyl or benzyl; or a physiologically acceptable acid addition salt thereof."

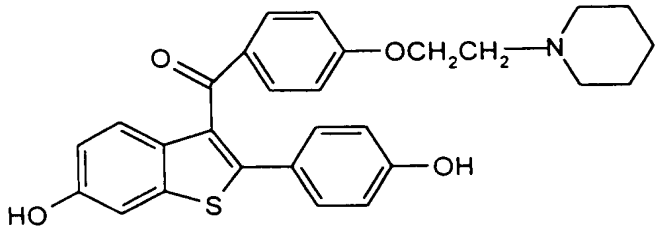
Raloxifene is that compound where R and R^1 are each hydrogen, therefore, claim 2 reads upon the approved product.

Claim 3 of the patent claims the "compound of claim 2 which is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof." 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene is raloxifene, thus, claim 3 reads upon the approved product.

Claim 5 of the patent claims a "compound of claim 2 wherein one of R and R^1 is hydrogen." Raloxifene is that compound where R and R^1 are each hydrogen, therefore, claim 5 reads upon the approved product.

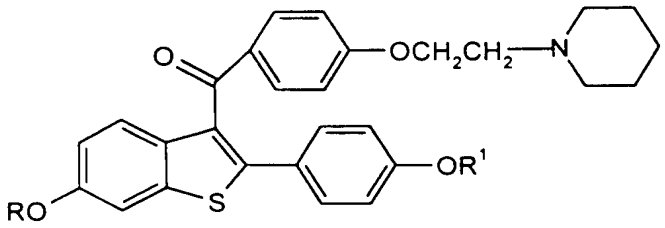
The approved product is in the form of a hydrochloride salt, which is identified at column 6, line 60, of the patent as a preferred pharmaceutically acceptable acid addition salt. Claim 18 of the patent claims a "compound of any one of claims 1 - 7 which is a physiological acceptable acid addition salt." Claim 19 of the patent claims a "compound of any one of claims 1 - 7 which is a hydrochloride." Therefore, the approved product is embraced by claims 18 and 19.

Claim 24 of the patent claims an "antiestrogenic and antiandrogenic pharmaceutical composition comprising a pharmaceutically acceptable diluent and an effective amount of a compound of the formula



a physiological acceptable ester or ether thereof, or a physiologically acceptable acid addition salt thereof." As this is the structure of raloxifene, claim 24 reads upon the approved product.

Claim 25 of the patent claims a "composition of claim 24 wherein the compound is of the formula



wherein R and R^1 independently are hydrogen, $-COR^2$ or R^3;
R^2 is hydrogen, C_1-C_{14} alkyl, C_1-C_3 chloroalkyl, C_1-C_3 fluoroalkyl, C_5-C_7 cycloalkyl, C_1-C_4 alkoxy, phenyl, or phenyl mono- or disubsubstituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl;
R^3 is C_1-C_4 alkyl, C_5-C_7 cycloalkyl or benzyl; or a physiologically acceptable acid addition salt thereof." Raloxifene is that compound where R and R^1 are each hydrogen, therefore, claim 25 reads upon the approved product.

Claim 26 of the patent claims a "composition of claim 25 wherein the compound is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof." 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene is raloxifene, thus, claim 26 reads upon the approved product.

As stated above, the approved product is in the form of a hydrochloride salt. Claim 27 of the patent claims a "composition of claim 26 wherein the compound is the hydrochloride." Therefore, the approved product is embraced by claim 27.

Claim 38 of the patent claims a "composition of claim 25 wherein one of R and R^1 is hydrogen." Raloxifene is that compound where R and R^1 are each hydrogen, therefore, claim 38 reads upon the approved product.

Accordingly, claims 1, 2, 3, 5, 18, 19, 24, 25, 26, 27, and 38 all read on the approved product.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug, the date a major health or environmental effects test on the drug was initiated and any available substantiation of that date or the date of an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; the date on which a new animal drug application (NADA) was initially submitted and the NADA number; and the date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product, the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; the date an application for a license was submitted under the Virus-Serum-Toxin Act; and the date the license issued;

(iv) For a patent claiming a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug, and Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published the Federal Register notice listing the additive for use;

(v) For a patent claiming a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available

substantiation of that date; the date on which the application for product approval or notice of completion of a product development protocol under section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application or protocol; and the date on which the application was approved or the protocol declared to be completed:

On April 26, 1992, Eli Lilly and Company, the assignee of U.S. Patent No. 4,418,068, submitted to the FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under Section 505(i) of the FFDCA to permit the interstate shipment of raloxifene hydrochloride for the purpose of conducting clinical studies to support the approval of a subsequent NDA for raloxifene hydrochloride. A copy of the letter transmitting the IND to the FDA is attached as Exhibit E. By letter dated May 1, 1992, the FDA acknowledged receipt of the IND, assigned the IND number 39503, and indicated that the IND would become effective thirty days after the date of its receipt on April 27, 1992. A copy of this letter is attached as Exhibit F. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as May 27, 1992, the effective date of an exemption under Section 505(i).

Lilly submitted a NDA pre-submission for raloxifene hydrochloride on March 13, 1997. This NDA pre-submission contained chemistry, manufacturing and control data and non-clinical pharmacology and toxicology data. This pre-submission did not include the entire NDA, so it did not start the statutory period for regulatory review. A copy of the letter submitting the NDA pre-submission is enclosed as Exhibit G. The NDA pre-submission was received by the FDA on March 17, 1997. A copy of the receipt letter dated March 17, 1997, for the NDA pre-submission from the FDA is included as Exhibit H.

Lilly submitted an NDA for raloxifene hydrochloride, NDA 20815, on June 8, 1997. A copy of the letter transmitting the NDA is attached as Exhibit I. The NDA submission was received by the FDA on June 9, 1997 as indicated by Exhibit J. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), June 9, 1997 is the date of initial submission of a new drug application under Section 505 for raloxifene hydrochloride.

The NDA described above was approved on December 9, 1997. Attached as Exhibit K is a letter dated December 9, 1997 from the FDA to Lilly approving the NDA for raloxifene hydrochloride. Thus, for the purpose of the "regulatory

review period" under 35 U.S.C. 156(g)(1), December 9, 1997 is the date of approval of the application for raloxifene hydrochloride submitted on June 8, 1997.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Lilly was actively involved in obtaining NDA approval for raloxifene hydrochloride. As discussed in (10) above, the IND for raloxifene hydrochloride was submitted on April 26, 1992, the NDA was submitted on June 8, 1997, and the NDA was approved on December 9, 1997. Lilly was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, Lilly had numerous contacts and meetings with the FDA with respect to the approval and, in fact, conducted additional studies at FDA's request to support the NDA approval. The description of significant activities undertaken by Lilly with respect to raloxifene hydrochloride during the regulatory review period as set forth in Exhibit L is illustrative of the activities involved.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 4,418,068 expires on April 3, 2001. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, Eli Lilly and Company (Assignment recorded on August 5, 1983, in Reel 4152, Frame 627). This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted within the sixty day period beginning on the date, December 9, 1997, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the December 9, 1997 letter from the FDA (Exhibit K), the product was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of raloxifene hydrochloride after regulatory review under Section 505 is the first permitted commercial marketing of raloxifene hydrochloride. This is confirmed by the absence

of any approved new drug application for raloxifene hydrochloride prior to December 9, 1997.

(b) Statement as to length of extension claimed:

The term of U.S. Patent No. 4,418,068 should be extended by 1103 days to April 10, 2004. This extension was determined on the following basis: as set forth in 35 U.S.C. 156(g)(1) and 37 C.F.R. 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND May 27, 1992 and the initial submission of the NDA June 9, 1997, a period of 1839 days, plus the length of time between the initial submission of the NDA June 9, 1997 to NDA approval December 9, 1997, a period of 183 days. These two periods added together equal 2022 days.

Pursuant to 35 U.S.C. 156(c) and 37 C.F.R. 1.775 (d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, the patent issued before the effective filing date of the IND, and therefore the regulatory review period is 2022 days as calculated above.

As discussed in paragraph (11) above and as illustrated in Exhibit L, Lilly was continuously and diligently working toward securing NDA approval for raloxifene hydrochloride. As Lilly acted with due diligence during the entire period of regulatory review, the 2022 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775 (d)(1)(ii).

Pursuant to 35 U.S.C. 156(c)(2) and 37 C.F.R. 1.775 (d)(1)(iii), this 2022 day period is to be reduced by one half of the time from the effective date of the initial IND May 27, 1992, or the date of patent issue, November 29, 1983, whichever is later, to the date of initial submission of the NDA, June 9, 1997, a period of 1839 days. One half of this period is 919 days. Thus, the 2022 day period is reduced by 919 days leaving a revised regulatory period of 1103 days.

Pursuant to 35 U.S.C. 156(c)(3) and 37 C.F.R. 1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval December 9, 1997 to April 3,

2001, (a period of 1211 days), when added to the revised regulatory review period (1103 days) exceeds 14 years (5113 days), the period of extension must be reduced so that the total of both such periods does not exceed fourteen years. In this case, the total of both such periods does not exceed 14 years and, therefore, the 1103 day revised regulatory review period is not reduced.

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. 156(g)(4) and 37 C.F.R. 1.775(d)(5-6). The patent to be extended issued before and clinical evaluation of the approved product began after the enactment of the statute, September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five year maximum on extension as provided in 35 U.S.C. 156(g)(6)(B) and 37 C.F.R. 1.775(d)(6) is applicable. In this case, the five year maximum exceeds the revised regulatory period, thus, the term of the patent is eligible for a 1103 day extension until April 10, 2004.

(13) A statement that applicant acknowledges a duty to disclose to the Assistant Commissioner for Patents and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (See §1.765):

Applicant acknowledges a duty to disclose to the Assistant Commissioner for Patents and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought. Further to the information already presented in this application and attached exhibits, applicant notes that on June 18, 1982, Eli Lilly and Company, the assignee of U.S. Patent No. 4,418,068, submitted to the FDA an IND for the purpose of conducting clinical studies to support the use of raloxifene hydrochloride as an antiestrogen agent. By letter dated June 21, 1982, the FDA acknowledged receipt of the IND and assigned the IND number 20486. As this IND was inactivated by Eli Lilly and Company via letters to the FDA dated September 26 and October 25, 1990, and is unrelied upon in the present

application, applicant asserts that this first IND is irrelevant to the present request for patent term extension.

(14) The prescribed fee for receiving and acting upon the application for extension (See §1.20(j)):

As indicated by the letter of transmittal submitted with this application, the Assistant Commissioner for Patents has been authorized to charge the filing fee of $1,120.00 to deposit account No. 05-0840 in the name of Eli Lilly and Company and any additional fees which may be required.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Address all correspondence to James J. Sales, Eli Lilly and Company, Patent Division/JJS, Lilly Corporate Center, Indianapolis, Indiana 46285. Direct telephone calls to James J. Sales, 317-276-3474.

(16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

(17) An oath or declaration as set forth in 37 C.F.R. 1.740(b):

As the undersigned agent of Eli Lilly and Company, the owner of record of U.S. Patent No. 4,418,068, which, by submission of this paper and attached Exhibits, now applies for an extension of term of this patent, I, David E. Boone, declare that (1) I am a Patent Attorney authorized to practice before the Patent and Trademark Office and have general authority from Eli Lilly and Company to act on its behalf in patent matters; that (2) I have reviewed and understand the contents of this application for extension of U.S. Patent No. 4,418,068; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. 1.710; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. 156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the

conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

I hereby appoint as United States attorneys to prosecute this request and to transact all business in the Patent and Trademark Office connected therewith: David E. Boone, Reg. No. 27,857, Robert A. Conrad, Reg. No. 32,089, and James J. Sales, said David E. Boone, Reg. No. 27,857 to have in addition full power of revocation, including the power to revoke the power herein granted to said Robert A. Conrad and James J. Sales.

ELI LILLY AND COMPANY

By: [signature]

David E. Boone
Assistant Secretary
Deputy General Counsel
General Patent Counsel
Registration No. 27,857
Phone: 317-276-3881

Eli Lilly and Company
Patent Division/JJS
Lilly Corporate Center
Indianapolis, Indiana 46285

Jan. 20, 1998

EXHIBIT A

Product Information Sheet for EVISTA®

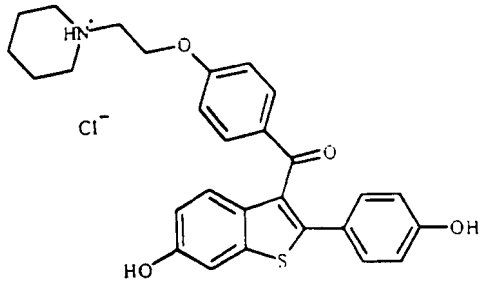
EVISTA®

Raloxifene Hydrochloride

60 mg Tablets

DESCRIPTION

EVISTA® (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical structure is



The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight of 510.05. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

EVISTA is supplied in a tablet dosage form for oral administration. Each EVISTA tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. This imbalance between resorption and formation is related to loss of estrogen, and may also involve age-related impairment of osteoblasts or their precursors.

Raloxifene reduces resorption of bone and decreases overall bone turnover. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, evidence from radiocalcium kinetics studies for decreased bone resorption and increases in bone mineral density (BMD).

Raloxifene's biological actions, like those of estrogen, are mediated through binding to estrogen receptors. This binding results in differential expression of multiple estrogen-regulated genes in different tissues. Recent data suggest that the estrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

Clinical data indicate that raloxifene, a selective estrogen receptor modulator (SERM), has estrogen-like effects on bone (increase in BMD) and on lipid (decrease in total and LDL cholesterol levels) metabolism. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissues. Preliminary clinical data (through 30 months) suggest EVISTA lacks estrogen-like effects on uterus and breast tissue.

Pharmacokinetics

The disposition of raloxifene has been evaluated in 276 postmenopausal women in conventional clinical pharmacology studies and in more than 1300 postmenopausal women in selected raloxifene trials. Raloxifene exhibits high within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. Table 1 summarizes the pharmacokinetic parameters of raloxifene.

Absorption

Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene (C_{max} 28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. EVISTA can be administered without regard to meals.

Distribution

Following oral administration of single doses ranging from 30 to 150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent.

Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex steroid binding globulin. In vitro, raloxifene did not interact with the binding of warfarin, phenytoin, or tamoxifen to plasma proteins.

Metabolism

Biotransformation and disposition of raloxifene in humans have been determined following oral administration of ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portions of the plasma concentration curves for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg•hr. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40 to 60 L/kg•hr. Increasing doses of raloxifene HCl (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

Excretion

Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates. In the osteoporosis prevention trials, raloxifene and metabolite concentrations are similar for women with estimated creatinine clearance as low as 23 mL/min.

Table 1. Summary of raloxifene pharmacokinetic parameters in the healthy postmenopausal woman

	C_{max}[a] (ng/mL)/ (mg/kg)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$[a] (ng•hr/mL)/ (mg/kg)	CL/F (L/kg•hr)	V/F (L/kg)
Single Dose					
Mean	0.50	27.7	27.2	44.1	2348
CV (%)	52	10.7 to 273[b]	44	46	52
Multiple Dose					
Mean	1.36	32.5	24.2	47.4	2853
CV (%)	37	15.8 to 86.6[b]	36	41	56

Abbreviations: C_{max} = maximum plasma concentration, $t_{1/2}$ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV = coefficient of variation

[a] Data normalized for dose in mg and body weight in kg

[b] Range of observed half-life

Special Populations

Geriatric—No differences in raloxifene pharmacokinetics were detected with regard to age (range 42 to 84 years).

Pediatric—The pharmacokinetics of raloxifene have not been evaluated in a pediatric population.

Gender—Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly different between age-matched female and male volunteers.

Race—Pharmacokinetic differences due to race have been studied on a limited basis in 1053 women consisting of 93.5% Caucasian, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race cannot be effectively determined.

Renal Insufficiency—Since negligible amounts of raloxifene are eliminated in urine, a study in patients with renal insufficiency was not conducted.

Hepatic Dysfunction—Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and total serum bilirubin ranging from 0.6 to 2.0 mg/dL. Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency (see WARNINGS).

Drug-Drug Interactions

Clinically significant drug-drug interactions are discussed in PRECAUTIONS.

Ampicillin—Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with coadministration of ampicillin. These reductions are consistent with decreased-enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. Therefore, EVISTA can be concurrently administered with ampicillin.

Antacids—Concurrent administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene.

Corticosteroids—The coadministration of EVISTA with corticosteroids has not been evaluated.

Cyclosporine—The coadministration of EVISTA with cyclosporine has not been evaluated.

Digoxin—Raloxifene has no effect on the pharmacokinetics of digoxin.

Animal Pharmacology

The skeletal effects of raloxifene treatment were assessed in ovariectomized rats and monkeys. In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy. There were positive effects of raloxifene on bone strength, but the effects varied with time. Cynomolgus monkeys were treated with raloxifene or conjugated estrogens for 2 years, equivalent at the bone level to approximately 6 years in humans. Raloxifene and estrogen increased BMD, but variability among animals obscured the ability to detect effects of either treatment on biomechanical strength. However, bone strength was positively correlated to BMD in both raloxifene- and estrogen-treated monkeys, indicating that BMD is a reasonable marker for bone strength.

Histologic examination of bone from rats and monkeys treated with raloxifene showed no evidence of woven bone, marrow fibrosis, or mineralization defects.

These results are consistent with data from human studies of radiocalcium kinetics and markers of bone metabolism, and are consistent with EVISTA's action as a skeletal antiresorptive agent.

Clinical Studies

Effects on Total Body and Regional Bone Mineral Density

In postmenopausal women, EVISTA preserves bone mass and increases BMD relative to calcium alone at 24 months. The effect on hip bone mass is similar to that for the spine. The relationships of BMD changes to skeletal fracture rates have not yet been established in EVISTA-treated women.

The effects of EVISTA on BMD in postmenopausal women were examined in three large randomized, placebo-controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these studies had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years postmenopause). The majority of the women were Caucasian (93.5%). Women were included if they had spine bone mineral density between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) for the 3 studies ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD. EVISTA, 60 mg administered once daily, produced increases in bone mass versus calcium supplementation alone, as reflected by dual-energy x-ray absorptiometric (DXA) measurements of hip, spine, and total body BMD. Compared with placebo, the increases in BMD for each of the 3 studies were statistically significant at 12 months and were maintained at 24 months (Table 2). The calcium-supplemented placebo groups lost approximately 1% of BMD over 24 months. See figures below for total hip results.)

Table 2. EVISTA (60 mg once daily) related increases in BMD for the three osteoporosis prevention studies expressed as mean percentage increase versus calcium-supplemented placebo at 24 months[a]

	Study		
Site	NA %	EU %	INT[b] %
Total Hip	2.0	2.4	1.3
Femoral Neck	2.1	2.5	1.6
Trochanter	2.2	2.7	1.3
Intertrochanter	2.3	2.4	1.3
Lumbar Spine	2.0	2.4	1.8

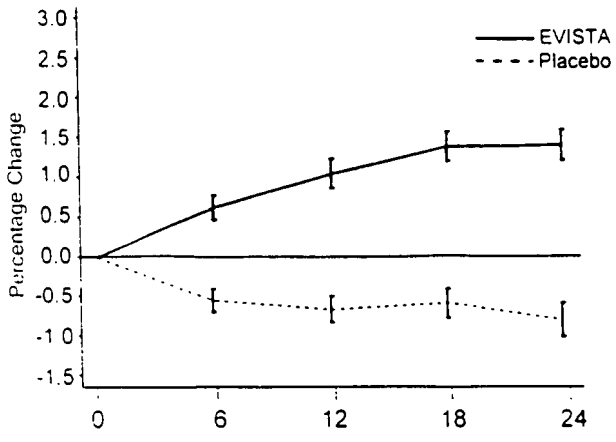
Abbreviations: NA = North American, EU = European, INT = International

[a] Intent-to-treat analysis, last observation carried forward

[b] All women in the study had previously undergone hysterectomy.

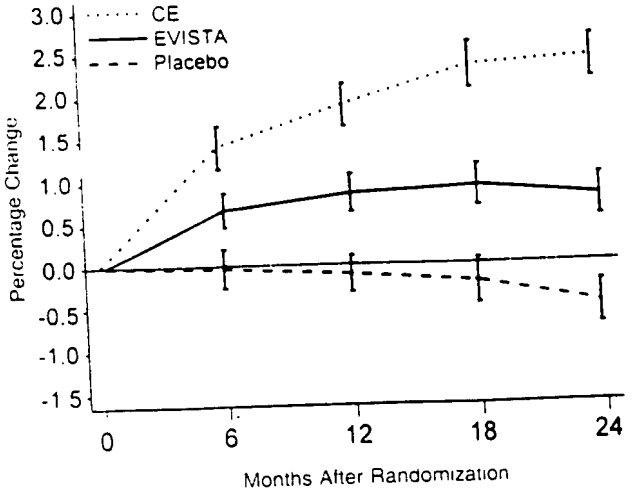
EVISTA also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of EVISTA on forearm BMD were inconsistent between studies. In Study EU, EVISTA prevented bone loss at the ultradistal radius, whereas in Study NA, it did not.

Total hip mean percentage change from baseline
All placebo and EVISTA subjects 24-month data from Studies NA and EU[a]



[a] Intent-to-treat analysis, last observation carried forward

Total hip mean percentage change from baseline
All placebo, EVISTA, and CE subjects 24-month data from Study INT (hysterectomized women)[a]



CE = conjugated estrogens 0.625 mg/day
[a] Intent to treat analysis, last observation carried forward

Assessments of Bone Turnover

In a 31-week open-label radiocalcium kinetics study, 33 early postmenopausal women were randomized to treatment with once-daily EVISTA 60 mg, cyclic estrogen/progestin (0.625 mg conjugated estrogens daily with 5 mg medroxyprogesterone acetate daily for the first two weeks of each month [HRT], or no treatment. Treatment with either EVISTA or HRT was associated with reduced bone resorption and a positive shift in calcium balance (-82 mg Ca/day and +60 mg Ca/day, respectively for EVISTA and -162 mg Ca/day and +91 mg Ca/day, respectively for HRT).

In the osteoporosis prevention trials, EVISTA therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, as reflected by changes in serum and urine markers of bone turnover (e.g., bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 24-month observation period.

Bone Histomorphometry

The tissue- and cellular-level effects of raloxifene were assessed by histomorphometric evaluation of human iliac crest bone biopsies taken after administration of a fluorochrome substance to label areas of mineralizing bone. The effects of EVISTA on bone histomorphometry were determined by pre- and post-treatment biopsies in a 6-month study of Caucasian postmenopausal women who received once-daily doses of EVISTA 60 mg or 0.625 mg conjugated estrogens. Ten raloxifene-treated and 8 estrogen-treated women had evaluable bone biopsies at baseline and after 6 months of therapy. Bone formation rate/bone volume and activation frequency, the primary efficacy parameters, decreased to a greater extent with conjugated estrogen treatment versus EVISTA treatment, although the differences were not statistically significant. Bone in EVISTA- and estrogen-treated women showed no evidence of mineralization defects, woven bone, or marrow fibrosis. In a blinded ongoing study, light microscopic evaluation of transiliac biopsies taken at baseline and after 2 years of therapy in 59 postmenopausal women receiving placebo, 60 mg-, or 120 mg-raloxifene hydrochloride showed no osteomalacia, osteocyte damage, woven bone, marrow fibrosis, or other abnormalities.

Effects on Lipid Metabolism

The effects of EVISTA on selected lipid fractions and clotting factors were evaluated in a 6-month study of 390 postmenopausal women. EVISTA was compared with oral continuous combined estrogen/progestin (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate, HRT) and placebo (Table 3). EVISTA decreased serum total and LDL cholesterol without effects on serum total HDL cholesterol or triglycerides. In addition, EVISTA significantly decreased serum fibrinogen and lipoprotein (a).

PHARMACIST—Please detach Patient Information sheet

Information for Patients

For safe and effective use of EVISTA, the physician should inform patients about the following:

Patient Immobilization—EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement during travel because of the increased risk of venous thromboembolic events.

Hot flashes or flushes—EVISTA is not effective in reducing hot flashes or flushes associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning EVISTA therapy.

Other Preventive Measures—Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the patient package insert before starting therapy with EVISTA and to re-read it each time the prescription is renewed.

Drug Interactions

Cholestyramine—Cholestyramine causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene and should not be coadministered with EVISTA.

Warfarin—The coadministration of EVISTA and warfarin has not been assessed under chronic conditions. However, 10% decreases in prothrombin time have been observed in single-dose studies. If EVISTA is given concurrently with warfarin, prothrombin time should be monitored.

Other Highly Protein-Bound Drugs—Raloxifene is more than 95% bound to plasma proteins. In vitro, raloxifene did not affect the binding of warfarin, phenytoin, or tamoxifen. Caution should be used when EVISTA is coadministered with other highly protein-bound drugs, such as clofibrate, indomethacin, naproxen, ibuprofen, diazepam, and diazoxide.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis:

In a 21-month carcinogenicity study in mice, there was an increased incidence of ovarian tumors in female animals given 9 to 242 mg/kg, which included benign and malignant tumors of granulosa/theca cell origin and benign tumors of epithelial cell origin. Systemic exposure (AUC) of raloxifene in this group was 0.3 to 34 times that in postmenopausal women administered a 60-mg dose. There was also an increased incidence of testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas in males given 41 or 210 mg/kg (4.7 or 24 times the AUC in humans), and prostatic leiomyoblastoma in males given 210 mg/kg.

In a 2-year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell origin was observed in females given 279 mg/kg (approximately 400 times the AUC in humans). The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and responsive to hormonal stimulation. The clinical relevance of these tumor findings is not known.

Mutagenesis:

Raloxifene HCl was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis with and without metabolic activation, the unscheduled DNA synthesis assay in rat hepatocytes, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, the in vivo sister chromatid exchange assay in Chinese hamsters, and the in vivo micronucleus test in mice.

Impairment of Fertility:

When male and female rats were given daily doses ≥5 mg/kg (≥0.8 times the human dose based on surface area, mg/m^2) prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg (16 times the human dose based on surface area, mg/m^2) for at least 2 weeks did not affect sperm production or quality, or reproductive performance. In female rats, at doses of 0.1 to 10 mg/kg/day (0.02 to 1.6 times the human dose based on surface area, mg/m^2), raloxifene disrupted estrous cycles and inhibited ovulation. These effects of raloxifene were reversible. In another study in rats in which raloxifene was given during the preimplantation period at doses ≥0.1 mg/kg (≥0.02 times the human dose based on surface area, mg/m^2), raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation and reduced litter size. The reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of raloxifene.

Pregnancy

Pregnancy Category X—EVISTA should not be used in women who are or may become pregnant (see CONTRAINDICATIONS).

Nursing Mothers—EVISTA should not be used by lactating women (see CONTRAINDICATIONS). It is not known whether raloxifene is excreted in human milk.

Pediatric Use—EVISTA should not be used in pediatric patients.

ADVERSE REACTIONS

The safety of raloxifene has been assessed primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin replacement therapy (HRT) control groups. The duration of treatment ranged from 2 to 30 months and 2036 women were exposed to raloxifene (371 patients received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received from 120 to 600 mg/day).

The majority of adverse events occurring during clinical trials were mild and generally did not require discontinuation of therapy. Therapy was discontinued due to an adverse event in 11.4% of 581 EVISTA-treated women and 12.2% of 584 placebo-treated women. Common adverse events considered to be drug-related were hot flashes and leg cramps (see Table 4). The first occurrence of hot flashes was most commonly reported during the first 6 months of treatment. Discontinuation rates due to hot flashes did not differ significantly between EVISTA and placebo groups (1.7% and 2.2%, respectively).

Adverse Events in Placebo-controlled Clinical Trials

Table 4 lists adverse events occurring in the placebo-controlled clinical trial database at a frequency ≥2.0% in either group and in more EVISTA-treated women than in placebo-treated women. Adverse events are shown without attribution of causality.

Table 3. EVISTA (60 mg once daily) and oral HRT effects on selected lipid fractions and factors in a 6-month study — Median percentage change from baseline

Endpoint	Treatment Group		
	EVISTA (N=95) %	HRT (N=96) %	PLACEBO (N=98) %
Total Cholesterol	-6.6[a]	-4.4[a]	0.9
LDL Cholesterol	-10.9[a]	-12.7[a]	1.0
HDL Cholesterol	0.7[b]	10.6[a]	0.9
HDL-2 Cholesterol	15.4[c]	33.3[a]	0.0
HDL-3 Cholesterol	-2.5[ab]	2.7	0.0
Fibrinogen	-12.2[ab]	-2.8	-2.1
Lipoprotein(a)	-4.1[ab]	-16.3[a]	3.3
Triglycerides	-4.1[b]	20.0[a]	-0.3
Plasminogen Activator Inhibitor-1	-2.1[b]	-29.0[a]	-9.4

Abbreviations: HRT = continuous combined estrogen-progestin (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate)
[a] Significantly different from placebo ($p<0.05$).
[b] Significantly different from HRT ($p<0.05$).

In the osteoporosis prevention studies (N=1764), 24-month data were consistent with results from the 6-month study. Compared with placebo, EVISTA significantly decreased serum total and LDL cholesterol by approximately 5% and 8% respectively, but did not affect HDL cholesterol or triglycerides.

Effects on the Uterus

In placebo-controlled osteoporosis prevention trials, endometrial thickness was evaluated every 6 months (for 24 months) by transvaginal ultrasonography (TVU). A total of 2978 TVU measurements were collected from 831 women in all dose groups. Endometrial thickness measurements in raloxifene-treated women were indistinguishable from placebo. There were no differences between the raloxifene-treated and placebo groups with respect to the incidence of reported vaginal bleeding.

In a 6-month study of 18 postmenopausal women that compared EVISTA to conjugated estrogens (0.625 mg/day [ERT]), endpoint endometrial biopsies demonstrated stimulatory effects of ERT, which were not observed for EVISTA. All samples from EVISTA-treated women showed nonproliferative endometria.

A 12-month study of uterine effects compared a higher dose of raloxifene HCl (150 mg/day) with HRT. At baseline, 43 raloxifene-treated postmenopausal women and 37 HRT-treated women had a nonproliferative endometrium. At study completion, endometria in all of the raloxifene-treated women remained nonproliferative whereas 13 HRT-treated women had developed proliferative changes. Also, HRT significantly increased uterine volume; raloxifene did not increase uterine volume. Thus, no stimulatory effect of raloxifene on the endometrium was detected at more than twice the recommended dose.

Effects on the Breast

Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. EVISTA was associated with significantly less breast pain and tenderness than reported by women receiving estrogens with or without added progestin (see ADVERSE REACTIONS and Table 5).

INDICATIONS AND USAGE

EVISTA is indicated for the prevention of osteoporosis in postmenopausal women.

The effects of EVISTA on fracture risk are not yet known.

Supplemental calcium should be added to the diet if daily intake is inadequate.

No single clinical finding or test result can quantify risk of postmenopausal osteoporosis with certainty. However, clinical assessment can help to identify women at increased risk. Widely accepted risk factors include Caucasian or Asian descent, slender body build, early estrogen deficiency, smoking, alcohol consumption, low calcium diet, sedentary lifestyle, and family history of osteoporosis. Evidence of increased bone turnover from serum and urine markers and low bone mass (e.g., at least 1 standard deviation below the mean for healthy, young adult women) as determined by densitometric techniques are also predictive. The greater the number of clinical risk factors, the greater the probability of developing postmenopausal osteoporosis.

CONTRAINDICATIONS

EVISTA is contraindicated in women who are or may become pregnant. EVISTA may cause fetal harm when administered to a pregnant woman. In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses ≥0.1 mg/kg (≥0.04 times the human dose based on surface area, mg/m^2), and hydrocephaly was observed in fetuses at doses ≥10 mg/kg (≥4 times the human dose based on surface area, mg/m^2). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses ≥1 mg/kg (≥0.2 times the human dose based on surface area, mg/m^2). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02 to 1.6 times the human dose based on surface area, mg/m^2) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed. The patient should be apprised of the potential hazard to the fetus if this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug.

EVISTA is contraindicated in women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.

EVISTA is contraindicated in women known to be hypersensitive to raloxifene or other constituents of the tablets.

WARNINGS

Venous Thromboembolic Events—An analysis of EVISTA-treated women across all placebo-controlled clinical trials showed an increased risk of venous thromboembolic events defined as deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. The greatest risk for thromboembolic events occurs during the first 4 months of treatment. EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and EVISTA therapy should be resumed only after the patient is fully ambulatory. Patients should be advised to avoid prolonged restrictions of movement during travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure and active malignancy.

Premenopausal Use—There is no indication for premenopausal use of EVISTA. Safety of EVISTA in premenopausal women has not been established and its use is not recommended (see CONTRAINDICATIONS).

Hepatic Dysfunction—Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and serum total bilirubin ranging from 0.6 to 2.0 mg/dL. Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with total bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with severe hepatic insufficiency.

PRECAUTIONS

General

Concurrent Estrogen Therapy—The concurrent use of EVISTA and systemic estrogen or hormone replacement therapy (ERT or HRT) has not been studied in prospective clinical trials and therefore concomitant use of EVISTA with systemic estrogens is not recommended.

Lipid Metabolism—EVISTA lowers serum total and LDL cholesterol by 6% to 11%, but does not affect serum concentrations of total HDL cholesterol or triglycerides.

These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemia.

Concurrent use of EVISTA and lipid-lowering agents has not been studied.

Endometrium—EVISTA has not been associated with endometrial proliferation (see **Clinical Studies** and ADVERSE REACTIONS). Unexplained uterine bleeding should be investigated as clinically indicated.

Breast—EVISTA has not been associated with breast enlargement, breast pain, or an increased risk of breast cancer (see **Clinical Studies** and ADVERSE REACTIONS). Any unexplained breast abnormality occurring during EVISTA therapy should be investigated.

Hot flashes—EVISTA [illegible] studied in women with a prior history of breast cancer.

Table 4. Adverse events occurring in placebo-controlled clinical trials at a frequency ≥2.0% and in more EVISTA-treated (60 mg once daily) women than placebo-treated women

Body System	EVISTA N=581 %	Placebo N=584 %
Body as a Whole		
Infection	15.1	14.6
Flu Syndrome	14.6	13.5
Leg Cramps	5.9	1.9
Chest Pain	4.0	3.6
Fever	3.1	2.6
Cardiovascular		
Hot Flashes	24.6	18.3
Migraine	2.4	2.1
Digestive		
Nausea	8.8	8.6
Dyspepsia	5.9	5.8
Vomiting	3.4	3.3
Flatulence	3.1	2.4
Gastrointestinal Disorder	3.3	2.1
Gastroenteritis	2.6	2.1
Metabolic and Nutritional		
Weight Gain	8.8	6.8
Peripheral Edema	3.3	1.9
Musculoskeletal		
Arthralgia	10.7	10.1
Myalgia	7.7	6.2
Arthritis	4.0	3.6
Nervous		
Depression	6.4	6.0
Insomnia	5.5	4.3
Respiratory		
Sinusitis	10.3	6.5
Pharyngitis	7.6	7.2
Cough Increased	6.0	5.7
Pneumonia	2.6	1.5
Laryngitis	2.2	1.4
Skin and Appendages		
Rash	5.5	3.8
Sweating	3.1	1.7
Urogenital		
Vaginitis	4.3	3.6
Urinary Tract Infection	4.0	3.9
Cystitis	3.3	3.1
Leukorrhea	3.3	1.7
Endometrial Disorder[a]	3.1	1.9

[a] Treatment-emergent uterine-related adverse event - including only patients with an intact uterus: EVISTA, n=354; Placebo, n=364.

Comparison of EVISTA and Hormone Replacement Therapy Adverse Events

EVISTA was compared with estrogen-progestin replacement therapy (HRT) in 3 clinical trials. Table 5 shows adverse events occurring more frequently in one treatment group and at an incidence ≥2.0% in any group. Adverse events are shown without attribution of causality.

Table 5. Adverse events reported in clinical trials with EVISTA (60 mg once daily) and continuous combined or cyclic estrogen plus progestin (HRT) at an incidence ≥2.0% in any treatment group[a]

Adverse Event	EVISTA (N=317) %	HRT-Continuous Combined (N=96) %	HRT-Cyclic (N=219) %
Urogenital			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding[b]	6.2	64.2	88.5
Digestive			
Flatulence	1.6	12.5	6.4
Cardiovascular			
Hot flashes	28.7	3.1	5.9
Body as a Whole			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest Pain	2.8	0	0.5

[a] These data are from both blinded and open-label studies.
[b] Treatment-emergent uterine-related adverse event - including only patients with an intact uterus: EVISTA, n=290; HRT-Continuous Combined, n=67; HRT-Cyclic, n=217.
Continuous Combined HRT = 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate.
Cyclic HRT = 0.625 mg conjugated estrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on days 1 through 14 or 17 through 28.

Laboratory Changes

The following changes in analyte concentrations are commonly observed during EVISTA therapy: increased apolipoprotein A1; and reduced serum total cholesterol, LDL cholesterol, fibrinogen, apolipoprotein B, and lipoprotein (a). EVISTA modestly increases hormone-binding globulin concentrations, including sex steroid-binding globulin, thyroxine-binding globulin, and corticosteroid-binding globulin with corresponding increases in measured total hormone concentrations. There is no evidence that these changes in hormone-binding globulin concentrations affect concentrations of the corresponding free hormones.

There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin which were generally of lesser magnitude than decreases observed during ERT/HRT. Platelet count was also decreased slightly and was not different from ERT.

Additional Safety Information

Incidences of estrogen-dependent carcinoma of the endometrium and breast are being evaluated across all completed and ongoing clinical trials involving 12,802 patients, of which approximately 8300 women have received at least one dose of raloxifene. The duration of exposure has been up to 39 months.

Endometrium—Compared to placebo, raloxifene did not increase the risk of endometrial cancer.

Breast—Compared to placebo, raloxifene did not increase the risk of breast cancer.

OVERDOSAGE

Incidents of overdose in humans have not been reported. In an 8-week study of 63 postmenopausal women, a dose of raloxifene HCl 600 mg/day was safely tolerated. No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg (810 times the human dose for rats and 405 times the human dose for mice based on surface area, mg/m^2) or in monkeys at 1000 mg/kg (80 times the AUC in humans). There is no specific antidote for raloxifene.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 60-mg EVISTA tablet daily which may be administered any time of day without regard to meals. The effect of EVISTA on BMD beyond two years of treatment is not known at this time, but is being evaluated in ongoing clinical trials.

HOW SUPPLIED

EVISTA 60-mg tablets are white, elliptical, and film coated. They are imprinted on one side with LILLY and the tablet code 4165 in edible blue ink. They are available as follows:

Bottle (count)	NDC Number
30	NDC - 0002-4165-30
100	NDC - 0002-4165-02
2000	NDC - 0002-4165-07

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

CAUTION—Federal (USA) law prohibits dispensing without prescription.

Literature issued December 9, 1997

Eli Lilly and Company, Indianapolis, IN 46285, USA

PRINTED IN USA

PV 3140 AMP

EXHIBIT B

U.S. Patent No. 4,418,068

4418068

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE

Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATION OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE **Letters Patent** ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof *I have hereunto set my hand and caused the seal of the* **Patent and Trademark Office** *to be affixed at the City of Washington this twenty-ninth day of November in the year of our Lord one thousand nine hundred and eighty-three, and of the Independence of the United States of America the two hundred and eighth.*

Attest:

Attesting Officer.

Commissioner of Patents and Trademarks.

United States Patent [19]

Jones

[11] **4,418,068**

[45] **Nov. 29, 1983**

[54] **ANTIESTROGENIC AND ANTIANDRUGENIC BENZOTHIOPHENES**

[75] Inventor: **Charles D. Jones**, Indianapolis, Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **331,042**

[22] Filed: **Dec. 16, 1981**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 246,335, Apr. 3, 1981, abandoned.

[51] **Int. Cl.**³ **A61K 31/445**; C07D 409/12

[52] **U.S. Cl.** **424/267**; 546/202; 546/237; 549/51

[58] **Field of Search** 546/202; 424/267

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Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Joseph A. Jones; Arthur R. Whale

[57] **ABSTRACT**

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, its ethers and esters, and the physiologically acceptable acid addition salts thereof, are valuable antiestrogens and antiendrogens.

62 Claims, No Drawings

ANTIESTROGENIC AND ANTIANDRUGENIC BENZOTHIOPHENES

CROSS-REFERENCE

This application is a continuation-in-part of application Ser. No. 246,335, filed Apr. 3, 1981, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of biochemistry, and provides pharmaceutical agents which are antiestrogens and antiandrogens.

Estrogen is transported throughout the body in the bloodstream and passively enters cells. However, only certain tissues exhibit responses to the hormone and are accordingly designated target tissues. These target tissues are characterized by specific estrogen receptors. The interaction of estradiol with estrogen receptors is an early event in a complex series of events which result in an estrogenic response. The uterus is considered the primary target tissue for estrogen. It is rich in estrogen receptors and exhibits dramatic growth under the influence of estradiol. Consequently the uterotropic response of rodents provides a reproducible model for the evaluation of estrogenic and antiestrogenic activity as well as the study of interactions with estrogen receptors.

A relationship has been established between estrogen sensitivity or dependency and the occurrence of estrogen receptors in certain mammary cancers as well as in benign fibrocystic disease of the breast. The neutralization of estrogen influence on those tissues is expected to benefit patients with those conditions by causing regression or preventing recurrence of the condition.

Antiestrogens antagonize the action of estrogens in animal models and display clinical efficacy in most mammary cancers which contain estrogen receptors. They interact with estrogen receptors, and elicit partial estrogenic response. Thus, the ability to antagonize the effect of estradiol is related to and restricted by the degree of intrinsic estrogenicity of the compound. The compound that evokes the greatest degree of estrogen antagonism, accordingly, is expected to be the most beneficial.

Similarly, androgen circulates and is taken up by androgen-receptive tissues. Prostatic cancer is a clinical condition believed to have androgen dependency or sensitivity, as does the condition known as benign prostatic hypertrophy. Accordingly, anti-androgens are in demand, and anti-androgenic testing is successfully carried out based on the rapid growth of the rodent prostate under the influence of androgen.

2. State of the Art

Antiestrogens have been under investigation for some years, and at least one such compound is presently being sold for palliative cancer therapy. This drug is tamoxifen, 1-(4-β-dimethylaminoethoxyphenyl)-1,2-diphenyl-but-1-ene.

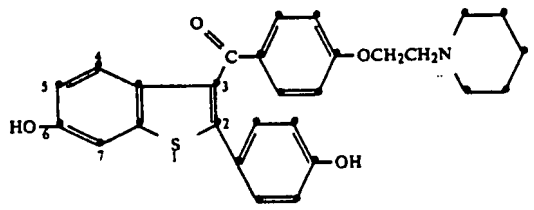
Another group of known antiestrogens are the dihydronaphthalenes of U.S. Pat. No. 4,230,862, of Suarez and Jones. The most important compound of this group is trioxifene mesylate, 2-[4-(2-pyrrolidinoethoxy)-benzoyl]-1-(4-methoxyphenyl)-3,4-dihydronaphthalene, methanesulfonic acid salt. Trioxifene has been clinically tested in cases of advanced breast cancer.

Another group of antiestrogens are the benzothiophenes of Jones and Suarez, U.S. Pat. No. 4,133,814. Tests of one of their compounds, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyrrolidinoethoxy)benzoyl]-benzo[b]thiophene, have been published by Black and Goode, Life Sciences 26, 1453–58 (1980). The same article also discussed similar tests of tamoxifen and trioxifene as estrogens and antiestrogens. The authors concluded that the above benzothiophene was considerably more effective as an antiestrogen, and considerably less estrogenic, than either tamoxifen or trioxifene.

SUMMARY OF THE INVENTION

This invention provides 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, having the formula

(I)



the physiologically acceptable esters and ethers thereof, and the physiologically acceptable acid addition salts thereof.

The compounds are antiestrogens and antiandrogens, and are used as pharmaceuticals for antiestrogen and antiandrogen therapy, especially in the treatment of mammary and prostatic tumors and in the treatment and prophylaxis of mammary and prostatic fibrocystic disease. Accordingly, pharmaceutical compositions and methods of antiestrogenic and anti-androgenic therapy are important parts of the invention. More particularly, the invention provides a method of alleviating a pathological condition of an endocrine target organ, which condition is dependent or partially dependent on an estrogen or on an androgen, which comprises administering an effective dose of a compound as described above to a subject suffering from such a condition or at risk of suffering from such a condition.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

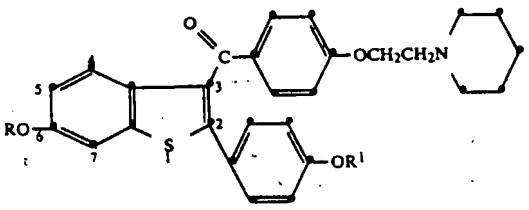
This invention provides a single benzothiophene compound and the physiologically acceptable esters and ethers which are formed on one or both of the hydroxy groups of the compound. The invention also provides physiologically acceptable salts of the compound in any of its forms.

Pharmaceutical chemists will easily recognize that physiologically active compounds which have accessible hydroxy groups are frequently administered in the form of physiologically acceptable esters or ethers. The literature concerning such compounds, such as estradiol, provides a great number of instances of such esters and ethers. The compound of this invention is no exception in this respect, but can be effectively administered as an ether or ester, formed on either one or both of the hydroxy groups, just as one skilled in pharmaceutical chemistry would expect. While the mechanism has not yet been investigated, it is believed that ethers and esters

are metabolically cleaved in the body, and that the actual drug, when such a form is administered, is the dihydroxy compound itself. It is possible, as has long been known in pharmaceutical chemistry, to adjust the rate or duration of action of the compound by appropriate choices of ester or ether groups. For example, the cycloalkyl ethers are known to increase the duration of action of many hydroxy-group-bearing physiologically active compounds.

Certain ether and ester groups are preferred as constituents of the compounds of this invention. The following formula shows the dihydroxy compound and the preferred ether and ester compounds.

(II)



wherein R and R^1 independently are hydrogen, $-COR^2$ or R^3;

R^2 is hydrogen, C_1–C_{14} alkyl, C_1–C_3 chloroalkyl, C_1–C_3 fluoroalkyl, C_5–C_7 cycloalkyl, C_1–C_4 alkoxy, phenyl, or phenyl mono- or disubstituted with C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl;

R^3 is C_1–C_4 alkyl, C_5–C_7 cycloalkyl or benzyl; and the physiologically acceptable acid addition salts thereof.

In this document, all measurements are expressed in weight units, unless otherwise stated, except that ratios of solvents are expressed in volume units.

The general chemical terms used in the formulae above have their usual meanings. For example, the terms C_1–C_{14} alkyl, C_1–C_4 alkoxy and C_1–C_4 alkyl include groups such as methyl, ethyl, isopropyl, butyl, s-butyl, tetradecyl, undecyl, neopentyl, 2,2-dimethylhexyl, 3-ethylnonyl, 3-butylheptyl, dodecyl, methoxy, propoxy and i-butoxy.

The terms C_1–C_3 chloroalkyl and C_1–C_3 fluoroalkyl include methyl, ethyl, propyl and isopropyl substituted to any desired degree with chlorine or fluorine atoms, from one atom to full substitution. The term C_5–C_7 cycloalkyl includes cyclopentyl, cyclohexyl and cycloheptyl.

The physiologically acceptable acid addition salts of the compounds of this invention may be formed of the dihydroxy compound itself, or of any of its esters or ethers, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. For example, salts may be formed with inorganic or organic acids such as hydrobromic acid, hydriodic acid, sulfonic acids including such agents as naphthalenesulfonic, methanesulfonic and toluenesulfonic acids, sulfuric acid, nitric acid, phosphoric acid, tartaric acid, pyrosulfuric acid, metaphosphoric acid, succinic acid, formic acid, phthalic acid, lactic acid and the like, most preferably with hydrochloric acid, citric acid, benzoic acid, maleic acid, acetic acid and propionic acid. It is usually preferred to administer a compound of this invention in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group such as the piperidino ring.

A group of representative compounds according to the invention will be mentioned by name, to assure that the reader of this document fully understands the compounds.

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, citrate

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-4-piperidinoethoxy)benzoyl]benzo[b]thiophene, lactate

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, sulfonate

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrogen sulfate

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, acetate

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, methanesulfonate

6-formyloxy-2-(4-formyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrobromide

6-hydroxy-2-(4-propionyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, nitrate

2-(4-hydroxyphenyl)-6-valeryloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, sulfate

2-(4-hydroxyphenyl)-6-(2,2-dimethylpropionyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, toluenesulfonate

6-hydroxy-2-(4-heptanoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, methanesulfonate

6-(2,3-dimethylbutyryloxy)-2-[4-(2,3-dimethylbutyryloxy)phenyl]-3-[4-(2-piperidinoethoxy)-benzoyl]-benzo[b]thiophene, lactate

6-nonanoyloxy-2-(4-nonanoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, dihydrogen phosphate

6-acetoxy-2-(4-undecanoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, phosphate

2-(4-hydroxyphenyl)-6-tridecanoyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, metaphosphate

2-(4-benzoyloxyphenyl)-6-pentadecanoyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydriodide

6-(2-methylpropionyloxy)-2-[4-(2-methylpropionyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, sulfonate

6-hydroxy-2-[4-(3-ethylhexanoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, acetate

6-(2-propylvaleryloxy)-2-[4-(2-propylvaleryloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, propionate

6-hydroxy-2-[4-(2,2-diethylheptanoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, formate

2-(4-propionyloxyphenyl)-6-(3-propylnonanoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, phthalate

6-hydroxy-2-[4-(5-butylundecanoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-(4-hydroxyphenyl)-6-trifluoroacetoxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

2-(4-butyryloxyphenyl)-6-trichloroacetoxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydriodide

2-(4-hydroxyphenyl)-6-(3,3,3-trifluoropropionyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-(3-chloropropionyloxy)-2-[4-(3-chloropropionyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, lactate

6-hydroxy-2-[4-(2,3-dichlorobutyryloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-[4-(2,3,4-trifluorobutyryloxy)phenyl]-6-(4-methoxybenzoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene

6-pentafluoropropionyloxy-2-(4-pentafluoropropionyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, citrate

6-heptachlorobutyryloxy-2-(4-heptachlorobutyryloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]-thiophene

6-cyclopentylcarbonyloxy-2-(4-cyclopentylcarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, toluenesulfonate

6-acetoxy-2-(4-cyclohexylcarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-hydroxy-2-(4-cycloheptylcarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-(4-hydroxyphenyl)-6-methoxycarbonyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, tartrate

6-benzoyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, phthalate

2-(4-hydroxyphenyl)-6-propoxycarbonyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrobromide

2-(4-hydroxyphenyl)-6-isobutoxycarbonyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, sulfate

6-ethoxy-2-(4-t-butoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, nitrate

6-(4-methylbenzoyloxy)-2-[4-(4-methylbenzoyloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene

6-hydroxy-2-[4-(2,4-diethylbenzoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, metaphosphate

6-hydroxy-2-[4-(3-methyl-5-propylbenzoyloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, picrate

6-(2,5-dibutylbenzoyloxy)-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, acetate

2-(4-hydroxyphenyl)-6-(4-methoxybenzoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, propionate

6-(3-isopropoxybenzoyloxy)-2-[4-(3-isopropoxybenzoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-(4-hydroxyphenyl)-6-(4-t-butoxybenzoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-benzoyloxy-2-[4-(3,5-diethoxybenzoyloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, formate

6-(4-hydroxybenzoyloxy)-2-[4-(4-hydroxybenzoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]-thiophene, methanesulfonate

6-(2,4-dihydroxybenzoyloxy)-2-[4-(2,4-dihydroxybenzoyloxy)phenyl]-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene

2-(4-hydroxyphenyl)-6-(2,4-dinitrobenzoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, lactate

6-(3-chlorobenzoyloxy)-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, toluenesulfonate

6-cyclopentoxy-2-[4-(2,4-dichlorobenzoyloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, methanesulfonate

2-(4-hydroxyphenyl)-6-(2,5-difluorobenzoyloxy)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-hydroxy-2-[4-(2-trifluoromethylbenzoyloxy)-phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

2-(4-acetoxyphenyl)-6-[3,5-bis(trichloromethyl)benzoyloxy]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

6-ethoxy-2-(4-ethoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo]b]thiophene, formate

6-hydroxy-2-(4-isopropoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, succinate

6-hydroxy-2-(4-butoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

6-s-butoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-(4-hydroxyphenyl)-6-cyclopentoxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydriodide

6-hydroxy-2-(4-cyclohexyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

2-(4-cycloheptyloxyphenyl)-6-propionyloxy-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, formate

6-benzyloxy-2-(4-benzyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

Certain classes of the compounds of this invention are preferred. The following paragraphs describe such preferred classes.

(a) R and R^1 are the same;

(b) one of R and R^1 is hydrogen;

(c) one or both of R and R^1 is $-COR^2$;

(d) one or both of R and R^1 is R^3;

(e) R^2 is alkyl;

(f) R^2 is chloroalkyl or fluoroalkyl;

(g) R^2 is cycloalkyl;

(h) R^2 is alkoxy;

(i) R^2 is phenyl;

(j) R^2 is substituted phenyl;

(k) R^3 is alkyl;

(l) R^3 is cycloalkyl;

(m) R^3 is benzyl;

(n) the compound is a free base;

(o) the compound is a salt;

(p) the compound is a hydrochloride.

It will be understood that the above classes may be combined to form additional preferred classes.

The compounds of this invention are made by a process which conveniently starts with a benzo[b]-thiophene having a 6-hydroxy group and a 2-(4-hydroxyphenyl) group.

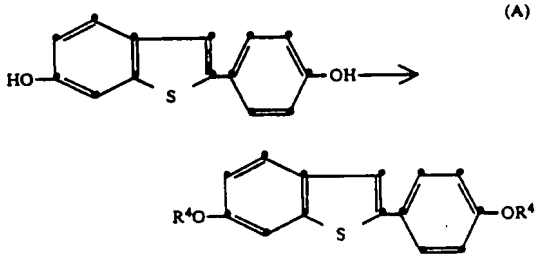
The starting compound is protected, acylated and deprotected to form the desired dihydroxy compound.

Biologically active ethers and esters may then be formed if desired. Other variations of the process are also conveniently used and will be explained below.

Protection

The first step in the usual synthesis is to protect the hydroxy groups, as indicated below.

(A)



wherein R^4 is R^3, $—COR^5$ or $—SO_2R^5$; R^5 is C_1–C_4 primary or secondary alkyl, C_1–C_3 fluoroalkyl, C_1–C_3 chloroalkyl, C_1–C_4 alkylphenyl, C_1–C_4 alkoxyphenyl, mono- or dinitrophenyl or mono- or di(chloro or fluoro)phenyl.

Alternatively, the 2-phenylbenzothiophene may be formed with R^3 protecting groups in place on the compound as it is synthesized, as illustrated below in Preparation 6. The R^3 groups are then kept in place on the compound throughout the process, as illustrated further below in Example 8.

The $—COR^5$ and $—SO_2R^5$ groups are placed on the dihydroxy compound according to methods known in the art. For example, when a $—COR^5$ group is desired, the dihydroxy compound is reacted with an acylating agent such as an acyl chloride, bromide, cyanide or azide, or with an appropriate anhydride or mixed anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, lutidine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine or the like. The reaction may also be carried out in an inert solvent such as ethyl acetate, dimethylformamide, dimethylsulfoxide, dioxane, dimethoxyethane, acetonitrile, acetone, methyl ethyl ketone or the like, to which at least one equivalent of an acid scavenger, such as a tertiary amine, has been added. Acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used, if desired. See, in general, Haslam, Tetrahedron 36, 2409-33 (1980). The acylation reactions which provide $—COR^5$ groups are carried out at moderate temperatures in the range of from −25° C. to 100° C.

Such acylations of the hydroxy groups may also be performed by acid-catalyzed reactions of the appropriate carboxylic acids, in inert organic solvents or neat. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid and the like are used.

The $—COR^5$ groups may also be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide and 1-hydroxybenzotriazole. See, for example, Bul. Chem. Soc. Japan 38, 1979 (1965), and Chem. Ber., 788 and 2024 (1970).

Other techniques are also known, such as by means of mixed anhydrides of the phosphorus compounds, Shioiri and Hamada, J. Org. Chem. 43, 3631-32 (1978); the use of 2-haloheterocyclic compounds such as 2-chloropyridine, Narasaka et al., Chem. Let., 763-66 (1977); and the use of thiol esters.

All of the above techniques of acylations which provide $—COR^5$ groups are carried out in solvents as discussed above. Those techniques which do not produce an acid product in the course of the reaction, of course, do not call for an acid scavenger in the reaction mixture.

Still other acylation methods are also useful, such as the use of an R^5-substituted ketene in an inert solvent, as discussed above, at a low temperature in the range of −30° C. to 25° C. Still further, the dihydroxy compound can be first converted to its dianion by treatment with a very strong base such as sodium hydroxide, sodium methoxide, potassium hydride, sodium hydride, n-butyllithium or the like, in order to obtain more complete reaction with the reagents which have been mentioned above. Acylation by the dianion technique is carried out in an inert solvent as described above, with no additional base or catalyst. The temperature of reactions according to the dianion technique is from −30° C. to 50° C.

When a $—SO_2R^5$-protected compound is desired, the dihydroxy starting compound is reacted with, for example, a derivative of the appropriate sulfonic acid, such as a sulfonyl chloride, bromide or sulfonyl ammonium salt, as taught by King and Manoir, J. Am. Chem. Soc. 97, 2566-67 (1975). The dihydroxy compound can also be reacted with the appropriate sulfonic anhydride. Such reactions are carried out under conditions such as were explained above in the discussion of reactions with acyl halides and the like.

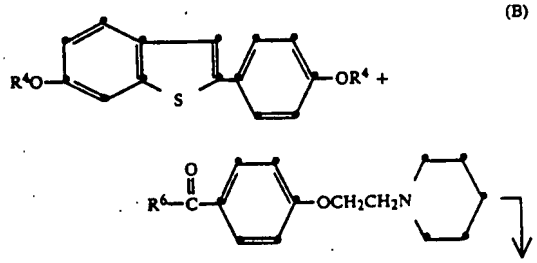
The $—SO_2R^5$ groups may also be provided by reaction of the dihydroxy compound with an appropriately substituted sulfene under conditions as discussed above for reactions with substituted ketenes. Still further, any of the sulfonate-producing reactions may be carried out on a dihydroxy compound in the dianion form, as discussed above.

It should be noted that the R^3 and $—COR^5$ groups used as protecting groups are within the scope of preferred biologically active groups, as discussed above, and thus it is entirely practical to use a given group as a protecting group in the synthesis, and to keep it in place on the product as an active ether or ester.

Acylation

The protected starting compound is acylated as the second step in the usual synthesis. The acylation can be done either with an acylating agent already containing the piperidinoethoxy group of the desired product, or with a precursor of it, as shown below.

(B)



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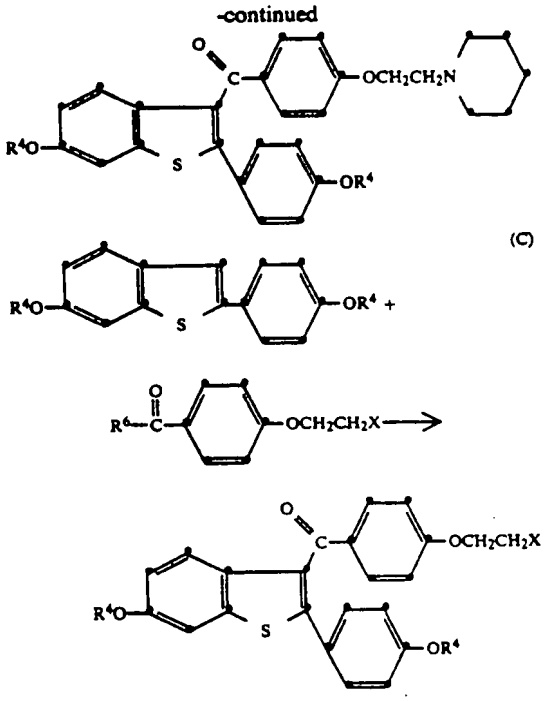


(C)

wherein X is bromo, chloro, iodo or $-OSO_2R^5$. The acylating agents are discussed in detail below.

The acylation of reactions B and C is a Friedel-Crafts acylation, and is carried out in the usual way. Either a Lewis acid or a proton acid may be used as the Friedel-Crafts catalyst; an excellent discussion of such catalysts appears in Olah, Friedel-Crafts and Related Reactions, Interscience Publ., New York, London and Sidney, 1963, vol. I, Ch. III and IV.

As explained by Olah, the classical Friedel-Crafts catalysts were Lewis acids. Such metal halides as aluminum chloride, aluminum bromide, zinc chloride, boron trifluoride, boron trichloride, boron tribromide, titanium tetrachloride, titanium tetrabromide, stannic chloride, stannic bromide, bismuth trichloride and ferric chloride are well known catalysts and are useful in this acylation, especially for acylations of reaction B. This proton acid catalysts are also useful for this acylation, especially for acylations of reaction C, and include such substances as phosphoric acid, polyphosphoric acid, perchloric acid, chlorosulfonic acid, alkylsulfonic acids such as methanesulfonic and ethanesulfonic acids, toluenesulfonic and benzenesulfonic acids, sulfuric acid, chloroacetic acid and trifluoroacetic acid. It is preferred to carry out the acylation with aluminum chloride or trifluoromethanesulfonic acid.

The acylation is ordinarily carried out in a solvent, and any inert organic solvent which is not significantly attacked by the conditions may be used. For example, halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and the like may be used, as can aromatics such as benzene, chlorobenzene and the like, alkanes such as petroleum ether, hexane and the like, and nitrohydrocarbons such as nitrobenzene and nitroalkanes.

It has been found that toluene is rather easily acylated under the conditions used in the Friedel-Crafts acylation step, and so it is important, when toluene is used in an earlier step of the process, to remove it as completely as possible from the protected starting compound, to avoid wasting the acylating agent.

The acylations may be carried out at temperatures from about the ambient temperature to about 100° C., preferably at the reflux temperature of the reaction mixture for processes catalyzed with the preferred proton acid, trifluoromethanesulfonic acid, and preferably at about ambient temperature for Lewis acid catalyzed processes.

The acylating agent used in the acylations B and C is an active form of the appropriate benzoic acid, wherein R^6 is one of the recognized "active groups", such as a chlorine atom, a bromine atom, or an activating ester. Appropriate activating esters are formed, as is well known, with hydroxybenzotriazole, dicyclohexylcarbodiimide and the like. The group R^6 may also indicate an anhydride, especially a mixed anhydride such as those formed with small carboxylic acids such as acetic acid, formic acid and especially sulfonic acids.

It is preferred, when the basic side chain is added according to reaction B above, to use as the acylating agent a small excess (1.05-1.5 molar) of the proper benzoyl halide, and to use, as the Friedel-Crafts catalyst, a slight molar excess of trifluoromethanesulfonic acid, or, alternatively, fluorosulfonic acid, p-toluenesulfonic acid, a dihalophosphoric acid or concentrated sulfuric acid. Alternatively, the reaction is also carried out in a preferred manner by using a substantial excess (1.5 to 3.5 molar) of the benzoyl halide in the presence of a large excess (2-12 molar) of aluminum chloride; other Lewis acid catalysts, such as aluminum bromide and the like may also be used.

In the case of acylations according to reaction C above, it is preferred to carry out the acylation in the presence of a strong acid such as was discussed immediately above. In this reaction, a full equivalent of acid is not necessary; a catalytic amount of acid is adequate. It is preferred to carry out the acylation steps in an inert halogenated solvent such as chloroform, dichloromethane, benzene, 1,2-dichloroethane and the like. In general, see as to such acylation reactions an article by Effenberger, Agnew. Chem. Int. Ed. Engl. 19, 151-230, especially 163-65 (1980).

Displacement

When the starting compound is acylated according to reaction C above, the piperidino group of the product is subsequently put in place by displacing the X group with piperidine. The X groups are leaving groups, which are easily displaced by an amine such as piperidine according to known methods.

For example, the displacement is carried out in an inert solvent such as ketones in the nature of acetone or methyl ethyl ketone, esters such as ethyl acetate and propyl formate, alcohols such as methanol or ethanol, nitriles such as acetonitrile, or amides such as dimethylacetamide and dimethylformamide, or in such inert solvents as hexamethylphosphoramide, and in the presence of an acid scavenger such as alkali metal carbonates and bicarbonates and the like. At least an equimolar quantity of acid scavenger is needed, and preferably a moderate excess. The displacement is carried out at ambient temperature, or may be carried out at moderately elevated temperatures from about ambient temperature to the reflux temperature of the reaction mixture.

More preferably, the displacement may be carried out in the additional presence of a catalytic amount of iodide ion, which acts as a catalyst for the displacement. When iodide is used in the mixture, the temperature range is lower, from about 0° C. to, preferably, the ambient temperature, although elevated temperatures are possible in some instances.

Further, the anion of piperidine may be formed before the reaction is carried out, as by contact with a very strong base such as sodium hydride or an alkyllithium compound. The use of an anion does not otherwise change the manner in which the displacement is carried out, except that an acid scavenger is not needed.

Deprotection

When a dihydroxy compound of this invention, of formula I above, is needed, it is obtained by cleaving the protecting groups, R^4, from the acylated compounds. Deprotection is carried out after displacement, when the 2-step acylation-displacement route is used. Both acyl and sulfonyl-protected compounds have been deprotected by simple hydrolysis with strong or moderately strong bases. For example, bases such as alkali metal hydroxides may be used for the hydrolysis, at temperatures from about the ambient temperature to about 100° C. At least two equivalents of base are needed, of course. Such hydrolyses are conveniently carried out in hydroxylic solvents, especially aqueous alkanols. The reactions may be also carried out, however, in any convenient solvent which leads itself to hydrolysis reactions, such as polyols including ethylene glycol, ethers such as tetrahydrofuran and the like, ketones such as acetone and methyl ethyl ketone and other polar water-miscible solvents such as dimethylsulfoxide. A preferred solvent system is a mixture of methanol and tetrahydrofuran, at ambient temperature. The cleavage may also be carried out with other bases, including, for example, sodium methoxide, potassium t-butoxide, hydrazine, hydroxylamine, ammonia, alkali metal amides and secondary amines such as diethylamine and the like. In some instances, when very strong bases are used, reaction temperatures in the range of from about 0° C. to the ambient temperature will give adequately rapid reaction rates.

The hydrolysis step lends itself well to reaction with the base in a 2-phase system with the assistance of a phase transfer catalyst. Such catalysts are now well known and are found among the tetraalkyl ammonium halides and among the crown ethers, such as dicyclohexyl-18-crown-6 ether.

In the case of compounds protected with —COR^5 groups, hydrolysis is readily carried out with acid catalysts, such as methanesulfonic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, a mixture of hydrobromic acid/acetic acid, or with acidic ion exchange resins. Such acid-catalyzed hydrolyses are carried out in hydroxylic solvents, such as water, alkanols, aqueous alkanols, or a mixture of tetrahydrofuran/methanol. It is preferred to carry out such hydrolyses at about the reflux temperature of the mixture, but, when particularly strong acids are used, temperatures as low as the ambient temperature are efficient.

A partially hydrolyzed compound is often desired, where only one of the hydroxy groups is deprotected. Such compounds may be prepared by any of the hydrolytic methods described above, by limiting the amount of base or the time of the reaction, or by lowering the temperature, so as to obtain less than complete hydrolysis. Such procedure usually produces a mixture of partially hydrolyzed compounds, which are separated by chromatography.

Basic hydrolysis in a primary or secondary alcohol solvent has been found to produce a relatively small amount of a mixture of compounds wherein one of the hydroxy groups has been hydrolyzed, and the other has been converted to an alkyl ether where the alkyl group is derived from the alcohol solvent. The major product of the reaction is the dihydroxy compound. Such monoethers are compounds of this invention, wherein one of R and R^1 is hydrogen and the other is an R^3 alkyl group derived from the alcohol.

When the starting compound was protected with R^3 alkyl, cycloalkyl or benzyl groups, the protecting groups are removed by known ether cleavage methods, most preferably in the presence of ethanethiol and aluminum chloride, as illustrated below in Example 8.

It has been found that the steps of displacement and cleavage of the protecting groups, R^4, can be combined to produce the dihydroxy compound in one step from an intermediate having a leaving group, X, on the side chain. Example 7 below illustrates such a step. The intermediate having the X group on the side chain is dissolved in a solvent which is suitable for processing at high temperature. Dimethylformamide is a particularly suitable solvent, as also is dimethylacetamide. Other solvents can be used as well, such as high-molecular-weight alkanes and halogenated alkanes having high boiling points. The intermediate is dissolved in the solvent, and piperidine is added, preferably with a catalytic amount of an iodide salt or a phase transfer catalyst to assist in the displacement reaction. The reaction mixture is stirred for a short time, such as a few hours, which serves to displace —X, and the mixture is then heated to an elevated temperature in the range of about 100°–150° C., with appropriate stirring, and preferably under an inert gas atmosphere. The R^4 protecting groups then hydrolyze to produce the desired dihydroxy compound in a single step.

Ethers and Esters

When it is desired to prepare a compound of this invention wherein one or both of R and R^1 is an ether group, the ether is prepared by placing the R^3 moiety on one or both of the hydroxy groups in a manner commonly used for the preparation of ethers. For example, the R^3 group may be added by reaction with an appropriate diazo compound, such as diazomethane, phenyldiazomethane or trimethylsilyldiazomethane (see Hashimoto et al., Tet. Let., 4619–22 (1980).) Such reactions are effectively carried out in solvents including esters such as ethyl acetate, halogenated solvents including dichloromethane and chloroform, and ethers including diethyl ether and tetrahydrofuran. Methanol or boron trifluoride is used as a catalyst, and the process is usually carried out at low temperatures from about −45° C. to about 0° C. Alternatively, alkylations may be carried out with the assistance of reagents such as trimethyloxosulfonium hydroxide, trimethylsulfonium hydroxide and trimethylselenonium hydroxide (all of which provide methyl groups), as taught by Yamauchi, Tet. Let., 1787–90 (1979). Alkylations with these reagents are carried out in solvents which are conducive to S_N2 displacements such as dimethylsulfoxide, dimethylformamide, hexamethylphosphoramide, acetone, acetonitrile and the like, usually at elevated temperatures

from about 40° C. to about the reflux temperature of the mixture.

Such alkylations may neatly be used to provide a mono-ether product, wherein one of R and R^1 is an R^3 alkyl group, by partially hydrolyzing the intermediate product, so that one of the R^4 protecting groups is left in place, alkylating, and completing the hydrolysis to remove the remaining R^4 group.

It is preferable, however, to prepare monoethers by using an ultimate starting compound in the mono-ether form, and using the ether group as a protecting group through the synthesis, protecting the other hydroxy with an acyl or sulfonyl group.

When a compound is desired wherein one or both of R and R^1 are —COR^2, it may often be most convenient to prepare the compound using an R^4 protecting group other than the desired —COR^2 group, hydrolyze off the protecting group and re-acylate one or both of the hydroxy groups at the end of the synthesis. Such acylations are carried out as described above in the discussion of —COR^2 groups as protecting groups. A particularly preferred condition for final acylations is to use tetrahydrofuran as the solvent and potassium carbonate as the acid scavenger for acylating agents such as acetic anhydride, benzyl chloride, ethyl chloroformate and the like. Another preferred reaction condition for very reactive acylating reagents such as trifluoroacetic anhydride is to use an equivalent of the corresponding acid (trifluoroacetic acid in the above instance) in tetrahydrofuran at about ambient temperature, and to add the acylating agent as the last addition to the reaction mixture.

Methyl-Protected Route

A particularly preferred route for preparing the dihydroxy compound of this invention is performed by preparing a dimethyl-protected benzothiophene starting compound, and acylating with the basic side chain according to a variation of reaction scheme B above. The methoxy groups are preferably cleaved with ethanethiol to prepare the dihydroxy compound in good yield, and without isolation of any of the intermediate products.

The methyl-protected starting compound is most easily obtained by a synthesis which is exemplified below in the first part of Preparation 6. The process is carried out by reacting 3-methoxybenzenethiol and α-bromo-4-methoxyacetophenone in the presence of a strong base at a relatively low temperature, to form α-(3-methoxyphenylthio)-4-methoxyacetophenone, which is then ring-closed with an agent such as polyphosphoric acid at a high temperature to obtain the desired starting compound.

The acylation is a Friedel-Crafts acylation, and is carried out in the usual way, using aluminum chloride or bromide, preferably the chloride, as the acylation catalyst.

The acylation is ordinarily carried out in a solvent, and any inert organic solvent which is not significantly attacked by the conditions may be used. For example, halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and the like may be used, as can aromatics such as benzene, chlorobenzene and the like. It is preferred to use a halogenated solvent, especially dichloromethane.

The acylations may be carried out at temperatures from about −30° C. to about 100° C., preferably at about ambient temperature, in the range of about 15° C. to about 30° C.

The acylating agent is an active form of the appropriate benzoic acid, wherein R^6 is a chlorine or bromine atom. The preferred acylating agent is that wherein R^6 is chloro.

The acyl chloride used as an acylating agent may be prepared from the corresponding carboxylic acid by reaction with a typical chlorinating agent such as thionyl chloride. Care must be taken to remove any excess chlorinating agent from the acyl chloride, however. Most conveniently, the acyl chloride is formed in situ, and the excess chlorinating agent is distilled off under vacuum.

Th stoichiometric amounts of the benzothiophene and the acylating agent may be used effectively. If desired, a small excess of either reactant may be added to assure that the other is fully consumed.

It is preferred to use a large excess of the acylation catalyst, such as about 2–12 moles per mole of product, preferably about 5–10 moles.

The acylation is rapid. Economically brief reaction times such as from about 15 minutes to a few hours provide high yields of the acylated intermediate. Longer reaction times may be used if desired but are not usually advantageous. As usual, the use of lower reaction temperatures calls for relatively long times.

The acylation step is ended, and the demethylation step begun, by adding to the reaction mixture a sulfur compound chosen from methionine and compounds of the formula R^7—S—R^8, wherein R^7 is hydrogen or unbranched C_1–C_4 alkyl, and R^8 is C_1–C_4 alkyl or phenyl.

The sulphur compounds are, most preferably, the alkylthiols, such as methanethiol, ethanethiol, the preferred agent, isopropanethiol, butanethiol and the like; dialkyl sulfides, such as diethyl sulfide, butyl s-butyl sulfide, ethyl propyl sulfide, butyl isopropyl sulfide, dimethyl sulfide, methyl ethyl sulfide and the like; benzenethiol; methionine; and alkyl phenyl sulfides such as methyl phenyl sulfide, ethyl phenyl sulfide, butyl phenyl sulfide and the like.

It has been found that the demethylation goes best when a substantial excess amount of the sulfur compound is used, in the range of from about 4 to about 10 moles per mole of the starting benzothiophene. The process can be carried out, although less efficiently, with a smaller amount of the sulfur compound in the range of about 2 or 3 moles per mole of starting compound. It is also possible to use a small amount of the sulfur compound, such as 2 or 3 moles per mole of starting compound, and to improve the yield by the addition of about 1 to 3 moles of an alkali metal halide, such as sodium, potassium or lithium chloride, iodide or bromide. (A similar effect of sodium iodide is shown by Niwa et al., Tet. Let. 22, 4239–40 (1981)).

The demethylation reaction goes well at about ambient temperature, in the range of from about 15° C. to about 30° C., and such operation is preferred. However, the demethylation step may be carried out at temperatures in the range of from about −30° C. to about 50° C. if it is desired to do so. Short reaction times in the range of about 1 hour have been found to be adequate.

After the product has been demethylated, it is recovered and isolated by conventional means. It is customary to add water to decompose the complex of the acylation catalyst; addition of dilute aqueous acid is advantageous. The product precipitates in many instances, or may be extracted with an organic solvent according to conventional methods.

The compounds of this invention, as discussed above, are very often administered in the form of acid addition salts. The salts are conveniently formed, as is usual in organic chemistry, by reacting the compound of this invention with a suitable acid, such as have been described above. The salts are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it.

All of the above reaction steps give acceptable yields when the stoichiometric amounts of the reactants are used, except as noted in certain specific steps above. As is normally the case in organic chemistry, improved yields are given by the use of an excess amount of one of the reactants, and it is practical to use an excess amount of the cheaper or the more easily obtained reactant. For example, in the formation of the protected starting compounds, it is practical and economical to use an excess of the acylating or sulfonating agent, to assure complete reaction of the more expensive dihydroxy starting compound. Excesses in the range of from about 1% to about 25% are conveniently used, when an excess of one reactant is desired.

The following preparations and examples further illustrate the synthesis of the compounds of this invention. The products described below were identified by various standard analytical techniques as stated in the individual preparations and examples. Nuclear magnetic resonance (nmr) analyses were run on a 100 mHz instrument in deuterochloroform unless otherwise stated.

The first preparation following illustrates the synthesis of an active form of a typical carboxylic acid for subsequent use as an acylating agent.

Preparation 1

4-(2-piperidinoethoxy)benzoic acid, hydrochloride

A 183 g. portion of methyl 4-(2-piperidinoethoxy)-benzoate was dissolved in 600 ml. of methanol, and 200 ml. of 5 N sodium hydroxide was added. The mixture was stirred at ambient temperature for 48 hours, the solvent was evaporated, and the residue was dissolved in 1 liter of water. The solution was cooled to below 10° C., and was acidified with cold 6 N hydrochloric acid. The product crystallized, and was collected by filtration and washed with methanol at −40° C. The solids were recrystallized from 3400 ml. of methanol to obtain 167 g. of the expected product, m.p. 274°-277° C.

The next four preparations illustrate the synthesis of protected starting compounds having various R^4 groups.

Preparation 2

6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene

Forty g. of 6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophene was dissolved in 800 ml. of anhydrous pyridine, and 41.6 g. of acetic anhydride and 100 mg. of 4-dimethylaminopyridine were added. The mixture was allowed to stand overnight at ambient temperature, and was then evaporated to an oily residue under vacuum. The residue was slurried with 3 liters of water with vigorous stirring, and the crystals which precipitated were collected by filtration and washed thoroughly with water. The solids were then dried at 80° C. under vacuum to obtain 52.5 g. of the acetyl-protected intermediate, m.p. 208°-210° C.

Preparation 3

6-benzoyloxy-2-(4-benzoyloxyphenyl)benzo[b]-thiophene

The synthesis was carried out according to the process of Preparation 2, except that 51.1 g. of benzoyl chloride was used instead of acetic anhydride. The product was 73.7 g. of the expected benzoyl-protected intermediate product in the form of white crystals, m.p. 216°-218° C.

Preparation 4

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)benzo[b]thiophene

Twenty g. of 6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophene was dissolved in 400 ml. of pyridine, together with 23.4 g. of methanesulfonyl chloride and 50 mg. of 4-dimethylaminopyridine. The mixture was stirred under a nitrogen blanket overnight at ambient temperature, and was then poured into 2 liters of water and stirred vigorously. The solids were collected by filtration, and washed successively with water, methanol and diethyl ether. The washed solids were then vacuum dried at 60° C. to obtain 32.5 g. of the desired intermediate product, m.p. 195°-197° C.

Preparation 5

6-benzenesulfonyloxy-2-(4-benzenesulfonyloxyphenyl)benzo[b]thiophene

The synthesis was carried out substantially according to Preparation 2 above, except that 64.1 g. of benzenesulfonyl chloride was used in place of acetic anhydride. The product was worked up as described in Preparation 2 to obtain 85 g. of the crude product, m.p. 138°-139° C., which was recrystallized twice from ¼ methanol-/ethyl acetate to obtain purified intermediate product, m.p. 146°-148° C.

Preparation 6

6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene

A 100 g. portion of 3-methoxybenzenethiol and 39.1 g. of potassium hydroxide dissolved in 300 ml. of water were added to 750 ml. of denatured ethanol, and the flask was put in a cooling bath. A total of 164 g. of α-bromo-4-methoxyacetophenone was then added in small portions, and the mixture was stirred for 10 minutes in the cooling bath after the addition was complete and then for 3 hours at ambient temperature. The solvent was then evaporated off in vacuum, and 200 ml. of water was added. The mixture was extracted with ethyl acetate, and the organic layer was washed twice with water, twice with aqueous sodium bicarbonate solution, and twice with aqueous sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered and evaporated under vacuum to obtain 202 g. of crude α-(3-methoxyphenylthio)-4-methoxyacetophenone, which was recrystallized from methanol and washed with hexane to obtain 158 g. of purified product, m.p. 53° C.

A 124 g. portion of the above intermediate was added in small portions to 930 g. of polyphosphoric acid at 85°

C. The temperature rose to 95° C. during the addition, and the mixture was stirred at 90° C. for 30 minutes after the addition was complete, and was then stirred an additional 45 minutes while it cooled without external heating. One liter of crushed ice was then added to the mixture, and an external ice bath was applied to control the temperature while the ice melted and diluted the acid. Five hundred ml. of additional water was added, and the light pink precipitate was filtered off and washed, first with water and then with methanol. The solids were dried under vacuum at 40° C. to obtain 119 g. of crude 6-methoxy-2-(4-methoxyphenyl)-benzo[b]-thiophene. The crude product was slurried in hot methanol, filtered, and washed with cold methanol, and the solids were recrystallized from 4 liters of ethyl acetate, filtered, washed with hexane and dried to obtain 68 g. of purified intermediate product, m.p. 187°-190.5° C.

Ninety g. of pyridine hydrochloride was added to a flask equipped with a distillation head, condenser and collecting flask, and was heated with stirring until the temperature in the distillation head was 220° C. The distillation apparatus was then removed, the pot was cooled to 210° C., and 30 g. of the abovepreprepared dimethoxy intermediate was added. The mixture was stirred at 210° C. for 30 minutes, and was then poured into 250 ml. of ice-water. The precipitate was extracted into 500 ml. of ethyl acetate, and the organic layer was washed with 150 ml. of saturated aqueous sodium bicarbonate and then with 150 ml. of saturated aqueous sodium chloride. The organic layer was then dried over magnesium sulfate, filtered and evaporated to dryness under vacuum to obtain 25.5 g. of the desired intermediate product, m.p. >260° C.

The next two examples illustrate acylations which produce compounds of this invention having acetyl and benzoyl R and R^1 groups, respectively.

EXAMPLE 1

6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

An acylating agent, in acid chloride form, was prepared by combining 26.3 g. of 4-(2-piperidinoethoxy)-benzoic acid, hydrochloride, 36.5 g. of thionyl chloride and 1 drop of dimethylformamide in 200 ml. of 1,2-dichloroethane, and stirring the mixture under reflux for 2 hours under a nitrogen atmosphere. The mixture was then evaporated to dryness under vacuum to obtain the desired 4-(2-piperidinoethoxy)benzoyl chloride, hydrochloride, which was dissolved in 1 liter of 1,2-dichloroethane. To the solution was added 20 g. of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene and the mixture was stirred vigorously. To it was then added, over about 3 minutes, 73.4 g. of aluminum chloride. During the addition, the reaction mixture turned dark brown and hydrogen chloride evolved. The mixture was then stirred for one hour, and was poured over 1 liter of ice-water. The layers were separated, and the aqueous layer was extracted three times with 200 ml. portions of warm chloroform. The organic layers were combined and dried over magnesium sulfate, and were then filtered and evaporated under vacuum to obtain a brownish-yellow oil, which are not purified. The presence of the desired product was confirmed by thin layer chromatography (TLC) on silica gel, eluting with 9/1 chloroform/methanol, which showed that the major constituent ran at the same R_f as authentic 6-acetoxy-2l-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene.

EXAMPLE 2

6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

The process of this example was run as was the process of Example 1, starting with the acid chloride formed from 18.9 g. of 4-(2-piperidinoethoxy)-benzoic acid, hydrochloride, and 20 g. of 6-benzoyloxy-2-(4-benzoyloxyphenyl)-benzo[b]thiophene. The reaction mixture was stirred for 1.5 hours, and was then worked up as described in Example 1 to obtain the desired product as an oil. A small portion of the crude product was crystallized from denatured ethanol to provide an analytical sample, m.p. 230°-233° C., the identity of which was confirmed by nmr analysis.

δ1.30-2.50 (6H, m, $NH(CH_2CH_2)CH_2$); 2.50-3.75 (6H, m, $NH(CH_2CH_2)_2CH_2$ and OCH_2CH_2N); 4.56 (2H, m, OCH_2CH_2N); 6.77 (2H, d, J=9 Hz, aromatic o to OCH_2); 7.10 (2H, d, J=9 Hz, aromatic o to OCO); 7.10-7.90 (17H, m, aromatic); 8.00-8.27 (6H, m, aromatic o to CO); 12.30-12.80 (1H, broad s, NH).

The next two preparations illustrate the acylation of sulfonyl-protected starting compounds.

Preparation 7

6-benzenesulfonyloxy-2-(4-benzenesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo-[b]thiophene, hydrochloride

An acid chloride was formed from 8.21 g. of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, as described in Example 1, and was combined with 10 g. of 6-benzenesulfonyloxy-2-(4-benzenesulfonyloxyphenyl)-benzo[b]thiophene in 500 ml. of 1,2-dichloroethane and treated with 22.9 g. of aluminum chloride. The mixture was stirred at ambient temperature overnight, and worked up as described in Example 1 above. The product was 15 g. of tan foam which would not crystallize. A 1 g. sample of the crude product was purified by column chromatography over a 4×20 cm. silica gel column, eluting first with chloroform, and then with 25% methanol in chloroform. The product-containing fractions were combined, treated with hydrochloric acid to form the hydrochloride salt, and evaporated to dryness under vacuum to provide the product as an oil, the identity of which was confirmed by an absorption maximum at 1645 cm^{-1} in its infrared spectrum, indicative of the —CO— function of the desired product. Its identity was further confirmed by its conversion to 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene in Example 6 below.

Preparation 8

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride

The acid chloride was formed from 2.0 g. of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, as described in Example 1, and was combined with 2 g. of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-benzo[b]thiophene in 50 ml. of dichloromethane. A 2.4 g. portion of trifluoromethanesulfonic acid was added, and the mixture was stirred overnight under reflux. The reaction mixture was then poured over ice and sodium bicarbonate solution, and the organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated under vacuum to a yellow foam, which was treated with excess 3% hydrogen chloride in

anhydrous methanol. The mixture was evaporated to dryness under vacuum to obtain a white foam which was dissolved in 18 ml. of boiling methanol. The solution was cooled to obtain 3.1 g. of the desired product, m.p. 128°–130° C., which was identified by nmr analysis.

δ1.50–2.00 (6H, m, N—(CH_2CH_2)$_2CH_2$); 2.57–3.75 (6H, m, NH(CH_2CH_2)$_2CH_2$ and OCH_2CH_2N); 3.36 (3H, s, CH_3SO_2); 3.46 (3H, s, CH_3SO_2); 4.45 (2H, broad t, J=6 Hz, OCH_2CH_2N); 6.97 (2H, d, J=9 Hz, aromatic o to OCH_2); 7.25–7.80 (8H, m, aromatic); 8.25 (1H, d, J=2 Hz, aromatic, o to O and S); 10.70–11.00 (1H, broad s, NH). Infrared absorption in KBr for the ketone CO appears at 1640 cm.$^{-1}$. Ultraviolet absorption maxima: λ_{max} (ε) in ethanol: 273 nm. (sh 26,000), 290 (29,500).

The next two preparations demonstrate the synthesis of intermediates which have leaving groups on the side chains.

Preparation 9

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-chloroethoxy)benzoyl]benzo[b]thiophene

The acid chloride was prepared from 1.1 g. of 4-(2-chloroethoxy)benzoic acid as described in Example 1, and the acid chloride was combined with 1.2 g. of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-benzo[b]thiophene in 25 ml. of 1,2-dichloroethane in the presence of 0.5 ml. of trifluoromethanesulfonic acid. The mixture was stirred under reflux for 2 hours and was then poured into ice-water. The organic layer was separated, extracted with sodium bicarbonate solution, dried over magnesium sulfate and concentrated under vacuum to obtain 1.9 g. of impure product. Chromatography over a 4×8 cm. silica gel column, eluting with 9/1 toluene/ethyl acetate gave 1.2 g. of impure intermediate product, which was recrystallized from methanol to provide white crystals, m.p. 123°–124° C. The absorption maximum for the CO function appeared at 1650 cm.$^{-1}$ in the infrared spectrum taken in chloroform.

Preparation 10

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-bromoethoxy)benzoyl]benzo[b]thiophene

One g. of 4-(2-bromoethoxy)benzoic acid was converted to the acid chloride, and was combined with 1.2 g. of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)benzo[b]thiophene, 20 ml. of dichloromethane and 0.5 ml. of trifluoromethanesulfonic acid. The mixture was stirred under reflux overnight, and was then poured into ice-water. The organic layer was separated, washed with sodium carbonate solution, dried and evaporated under vacuum to obtain 2.1 g. of brown oil. The oil was chromatographed over a 4×8 cm. silica gel column with 9/1 toluene/ethyl acetate and the product-containing fractions were combined and evaporated under vacuum to obtain 1.8 g. of purified product as an oil. The product was identified by its MH^+ molecular ion, m/e 626, in the field desorption mass spectrum and by an absorption maximum in the infrared spectrum, in chloroform, at 1645 cm.$^{-1}$ attributable to the CO function. A small sample was recrystallized from methanol to obtain white crystals, m.p. 105°–107° C.

The following two preparations illustrate the displacement of side chain leaving groups with piperidine.

Preparation 11

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride

A 1.5 g. portion of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-bromoethoxy)benzoyl]benzo[b]thiophene was combined with 5 ml. of piperidine, 25 ml. of anhydrous dimethylformamide and 150 mg. of potassium iodide. The mixture was stirred at ambient temperature for two hours, and was then evaporated to dryness under vacuum. To the residue was added 25 ml. of saturated aqueous sodium bicarbonate and the mixture was extracted with two 25 ml. portions of ethyl acetate. The organic layers were combined and washed five times with 20 ml. portions of aqueous sodium chloride, dried over magnesium sulfate and evaporated under vacuum to a brown oil. To the oil was added 50 ml. of 3% hydrogen chloride in methanol, and the mixture was evaporated to dryness again. To it was added 10 ml. of methanol, and the mixture was warmed and evaporated down to about 8 ml. It was then cooled, and the purified intermediate product, m.p. 128°–130° C., precipitated. About 1.6 g. of purified intermediate product was obtained.

Preparation 12

6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

An 0.58 g. portion of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-chloroethoxy)-benzoyl]benzo[b]thiophene was combined with 20 ml. of dimethylformamide, 4.8 ml. of piperidine and 100 mg. of potassium iodide, and the mixture was stirred overnight at 40° C. and then at 50° C. for two hours. The mixture was evaporated to a brown oil under vacuum, and the oil was worked up by pouring it into 50 ml. of saturated aqueous sodium bicarbonate and extracting the mixture twice with 40 ml. portions of ethyl acetate. The organic layers were combined, washed twice with 100 ml. portions of saturated aqueous sodium chloride and concentrated under vacuum to an oil. To the oily residue was added 50 ml. of 3% hydrogen chloride in methanol, and the acidic mixture was concentrated again to an oil, which was dissolved in hot denatured ethanol and crystallized. The first crop of purified crystals amounted to 0.4 g. and had a melting point and infrared and ultraviolet spectra identical to those of the products of Preparations 8 and 11.

The next four examples illustrate the preparation of dihydroxy compounds of this invention by the hydrolysis of the protected compounds which have been prepared above.

EXAMPLE 3

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

A 4 g. portion of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene, hydrochloride, was combined with 100 ml. of denatured alcohol and 10 ml. of 5 N sodium hydroxide, and stirred under reflux for 1.5 hours under a nitrogen atmosphere. The reaction mixture was then evaporated to dryness under vacuum, and the residue was dissolved in 200 ml. of water and washed with 300 ml. of diethyl ether. The water layer was degassed under vacuum, and then nitrogen was

bubbled through it to remove all traces of ether. The mixture was then acidified with 1 N hydrochloric acid, and then made basic with excess sodium bicarbonate. The precipitate was collected by filtration and washed with cold water to obtain 2.4 g. of crude product. It was purified on a 2×30 cm. column of silica gel, eluting first with 700 ml. of 5% methanol in chloroform, followed by 1 liter of 10% methanol in chloroform. The impurities came off first, and the product-containing fractions were combined and evaporated under vacuum to obtain 1.78 g. of yellow oil. The oil was dissolved in 6 ml. of acetone, seeded and chilled in a freezer to obtain 1.2 g. of purified product, m.p. 143°–147° C. The identity of the product was confirmed as follows:

nmr spectrum (100 mHz in dmso-d_6) δ1.20–1.65 (6H, m, $N(CH_2\underline{CH_2})_2\underline{CH_2}$); 2.30–2.45 (4H, m, $N(\underline{CH_2}CH_2)_2CH_2$); 2.60 (2H, t, J=6 Hz, $OCH_2\underline{CH_2}N$); 4.06 (2H, t, J=6 Hz, $OC\underline{H_2}CH_2N$); 6.68 (2H, d, J=9H, aromatic o to OH); 6.85 (1H, q, $J_{H4\text{-}H5}$=9 Hz, $J_{H5\text{-}H7}$=2 Hz, H5 of benzothiophene ring); 6.90 (2H, d, J=9 Hz, aromatic o to OCH_2CH_2N); 7.18 (2H, d, J=9 Hz, aromatic m to OH); 7.25 (1H, d, J=9 Hz, H4 of benzothiophene ring); 7.66 (2H, d, J=9 Hz, aromatic o to CO); 9.72 (2H, broad s, OH). Ultraviolet spectrum in ethanol: λ_{max} (ε): 290 nm. (34,000). Electron impact mass spectrum M+ at m/e 473.

EXAMPLE 3A

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

A 3.6 g. portion of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene was dissolved in 100 ml. of tetrahydrofuran and 40 ml. of methanol, and 10 ml. of 5 N sodium hydroxide was added. The mixture was stirred for 16 hours at ambient temperature, and was then worked up by the procedure of Example 3 above to obtain 3.5 g. of a yellow solid. The impure product was purified by column chromatography on silica gel, eluting with a gradient solvent from 5% methanol in chloroform to 30% methanol in chloroform. The product-containing fractions were evaporated to obtain 1.85 g. of oily product, which was recrystallized from acetone to obtain 1.25 g. of purified product, m.p. 141°–144° C.

EXAMPLE 4

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The oily product of Example 1 above, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride, was dissolved in 700 ml. of methanol and 100 ml. of 5 N sodium hydroxide. The mixture was stirred at ambient temperature for two hours, and was then evaporated to an oil under vacuum at a temperature below 40° C. The residue was dissolved in 500 ml. of water and washed twice with 500 ml. portions of diethyl ether. The aqueous layer was acidified to pH 2 with cold 50% aqueous methanesulfonic acid, diluted to about 3 liters, and washed twice with 1 liter portions of diethyl ether. The aqueous layer was then separated, thoroughly degassed under vacuum, and made basic with aqueous ammonia. The resulting solids were collected by filtration and vacuum dried at 40° C. to obtain 14.2 g. of crude product which was chromatographed over a 5×5 cm. column of Activity I silica gel, eluting with 15% methanol in chloroform. The product-containing fractions were evaporated to dryness to obtain a yellow foam, which was recrystallized from acetone to obtain 11.9 g. of product, which was substantially identical to the product of Example 3 above by nmr, ultraviolet and infrared analysis.

EXAMPLE 5

6-hydroxy-2-(4-hyroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The crude product of Example 2 above, 6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride, was combined with 400 ml. of ethanol, 400 ml. of water and 55 ml. of methanesulfonic acid. The mixture was stirred on the steam bath for 72 hours, and was then evaporated down to an oil which was diluted to about 6 liters with water. The aqueous solution was washed twice with 1 liter portions of diethyl ether, and was then thoroughly degassed under vacuum, cooled to about 20° C., and made basic with aqueous ammonia to pH 8.4. The product which precipitated was collected by filtration and vacuum dried, and was then recrystallized from about 80 ml. of acetone. The product was vacuum dried at 40° C. to obtain 18.1 g. of crystals which was found by nmr, mass spectrum, infrared and ultraviolet analysis to be substantially identical to the product of Example 3.

EXAMPLE 6

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The oily 6-benzenesulfonyloxy-2-(4-benzenesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, hyrochloride, which was prepared in Preparation 6 above was added to 300 ml. of denatured ethanol and 30 ml. of 5 N sodium hyroxide under a nitrogen atmosphere, and stirred under reflux for two hours. The mixture was then evaporated under vacuum, and the residue was dissolved in 600 ml. of water, which was washed with 800 ml. of diethyl ether. The aqueous layer was made acid to pH 2.0 with methanesulfonic acid, diluted to 6 liters with additional water, and washed twice with 2-liter portions of diethyl ether. The aqueous layer was degassed under vacuum, and made basic to pH 8.4 with aqueous ammonia. The resulting yellow-brown crystals were collected, washed with water and vacuum dried at 40° C., to obtain 7.4 g. of the expected product. A final recrystallization of the product from acetone provided light tan crystals which by nmr, infrared, and ultraviolet spectra were substantially identical to the desired product prepared in Example 3 above.

The next example illustrates a synthesis of the dihydroxy compound of this invention from an intermediate having a leaving group on the side chain by displacement of the leaving group with piperidine and cleavage of the protecting groups in a single step.

EXAMPLE 7

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

A 1.5 g. portion of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-(4-bromoethoxybenzoyl)-benzo[b]thiophene, hydrochloride, was combined with 25 ml. of dimethylformamide, 5 ml. of piperidine and 150 mg. of potassium iodide, and was stirred for two hours at ambient temperature. The reaction was then heated to 110° C. in an oil bath, under a nitrogen atmosphere, and stirred for 5 days. The course of the reaction was followed by thin layer chromatography on

silica gel plates, using a 9/1 mixture of chloroform/methanol as the eluting solvent. As the reaction went on, the spot indicating the protected comopund gradually disappeared, and was replaced, first by spots indicating the two possible mono-protected compounds, and then by a spot indicative of the desired product.

EXAMPLE 8

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

Under a nitrogen blanket, a mixture of 3 g. of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, 2 drops of dimethylformamide, 2.5 ml. of thionyl chloride and 40 ml. of chlorobenzene was heated at 70°–75° C. for about one hour. The excess thionyl chloride and 15–20 ml. of solvent were then distilled off. The remaining suspension was cooled to ambient temperature, and to it were added 100 ml. of dichloromethane, 2.7 g. of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene and 10 g. of aluminum chloride. The solution was stirred for about one hour, 7.5 ml. of ethanethiol was added, and the mixture was stirred for 45 minutes more. Then 40 ml. of tetrahydrofuran was added, followed by 15 ml. of 20% hydrochloric acid, with an exotherm to reflux. Fifty ml. of water and 25 ml. of saturated aqueous sodium chloride was added. The mixture was stirred and allowed to cool to ambient temperature. The precipitate was collected by filtration and washed successively with 30 ml. of water, 40 ml. of 25% aqueous tetrahydrofuran, and 35 ml. of water. The solids were then dried at 40° C. under vacuum to obtain 5.05 g. of product, which was identified by nmr.

δ1.7 (6H, m, $N(CH_2\underline{CH_2})_2\underline{CH_2}$); 2.6–3.1 (2H, m, $\underline{NCH_2}$); 3.5–4.1 (4H, m, $\underline{NCH_2}$); 4.4 (2H, m, $\underline{OCH_2}$); 6.6–7.4 (9H, m, aromatic); 7.7 (2H, d, aromatic o to CO); 9.8 (2H, m, OH).

The following group of examples illustrates the preparation of ester derivatives of this invention from the dihydroxy compound.

EXAMPLE 9

6-trifluoroacetoxy-2-(4-trifluoroacetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, trifluoroacetate

One g. of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene was dissolved in 10 ml. of tetrahydrofuran and combined with 0.25 ml. of trifluoroacetic acid and 1 ml. of trifluoroacetic anhyride. The mixture was stirred for 5 minutes, and then was evaporated to a pale green oil under vacuum at 40° C. A field desorption high resolution mass spectrum showed m/e 665.128, correct for the desired diester. An infrared spectrum in deuterochloroform showed a strong absorption at 1800 cm.$^{-1}$ attributable to the CF_3CO_2 carbonyl in addition to the ketone carbonyl absorption at 1650 cm.$^{-1}$.

Further observation of the product after several days indicated that some hydrolysis of one or both ester groups had occurred.

EXAMPLE 10

6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

Two g. of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene was dissolved in 30 ml. of tetrahydrofuran, and 3.5 g. of potassium carbonate was added. The vessel was blanketed with nitrogen and 0.9 g. of acetic anhydride was added. The mixture was stirred at ambient temperature for 2 hours, and then under reflux for 2 hours more. The mixture was then cooled, and to it was added 200 ml. of chloroform. The mixture was washed with 100 ml. of aqueous sodium chloride solution, and the organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under vacuum at 40° C. A white foam was obtained, which was determined to be the desired product.

nmr spectrum: δ1.50 (6H, m, $N(CH_2\underline{CH_2})_2CH_2$); 2.24 (3H, s, CH_3CO); 2.32 (3H, s, CH_3CO); 2.46 (4H, broad t, J=5 Hz, $N(\underline{CH_2}CH_2)_2CH_2$); 2.72 (2H, t, J=7 Hz, $OCH_2\underline{CH_2}N$); 4.06 (2H, t, J=7 Hz, $O\underline{CH_2}CH_2N$); 6.74 (2H, d, J=9 Hz, aromatic o to OCH_2); 6.95 (2H, d, J=9 Hz, aromatic o to $OCOCH_3$); 7.05 (1H, q, $J_{H4\text{-}H5}$=9 Hz and $J_{H5\text{-}H7}$=2 Hz, H5 of the benzothiophene ring); 7.42 (2H, d, J=9 Hz, aromatic m to $OCOCH_3$); 7.70 (2H, d, J=9 Hz, aromatic o to CO). The signals for H4 and H7 of the benzothiophene ring were somewhat obscured by other peaks, but appeared between δ7.75 and 7.80. The infrared spectrum in chloroform showed a strong maximum at 1760 cm.$^{-1}$, attributable to the acetate ester groups. The high resolution mass spectrum showed m/e 557.186.

EXAMPLE 11

6-dodecanoyloxy-2-(4-dodecanoyloxyphenyl)3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The process of this example was carried out as described above in Example 10, using 1.9 g. of lauroyl chloride as the acylating agent. The evaporation of the washed reaction mixture gave an oil, which was purified by chromatography over a 2 inch×3 inch silica gel column eluted with 19/1 chloroform/methanol. The product-containing fractions were combined and concentrated under vacuum at 40° C. for 12 hours to obtain an oily solid, which was confirmed to be the desired product by a strong absorption at 1750 cm.$^{-1}$ on the infrared spectrum in chloroform, attributable to the ester carbonyl groups. The field desorption mass spectrum showed the correct molecular ion, m/e 837.494, for the desired product. The nmr spectrum was poorly resolved.

EXAMPLE 12

6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The process of this reaction was carried out as described above in Example 10, using 1.0 g. of ethyl chloroformate as the acylating agent. The evaporation of the washed reaction mixture provided a pale green oil, which was confirmed to be the desired product by the carbonyl absorption at 1762 cm.$^{-1}$ in the infrared spectrum in chloroform. The high resolution mass spectrum showed m/e 617.207. The nmr spectrum was consistent with the structure.

δ1.36 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$); 1.41 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$); 1.63 (6H, m, $N(CH_2\underline{CH_2})_2CH_2$); 2.61 (4H, m, $N(\underline{CH_2}CH_2)_2CH_2$); 2.85 (2H, t, J=7 Hz, $OCH_2\underline{CH_2}N$); 4.17 (2H, t, J=7 Hz, $O\underline{CH_2}CH_2N$); 4.28 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$); 4.34 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$); 6.75 (2H, d, J=9 Hz, aromatic o to OCH_2CH_2N); 7.05 (2H, d, J=9 Hz, aromatic o to $OCO_2C_2H_5$); 7.15 (1H, q, J=9 Hz, J=2 Hz, H5 of benzothiophene ring); 7.44 (2H, d, J=9 Hz, aromatic m to $OCO_2C_2H_5$); 7.63 (1H, d, J=9 Hz, H4 of benzothiophene ring); 7.72 (2H, d, J=9 Hz,

aromatic o to CO); 7.73 (1H, d, J=2 Hz, H7 of benzothiophene ring).

EXAMPLE 13

6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

A 2 g. portion of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene was suspended in 35 ml. of chloroform, and 3.5 g. of potassium carbonate was added. The flask was blanketed with nitrogen, and 2 mg. of 4-dimethylaminopyridine and 1.2 g. of benzoyl chloride were added. The mixture was heated in an 80° C. oil bath for 4 hours under reflux, and was then poured into a large amount of aqueous sodium chloride solution. The mixture was then extracted three times with 50 ml. portions of chloroform, and the organic layers were combined and washed with aqueous sodium chloride solution and dried over magnesium sulfate. The solution was then filtered, and hydrogen chloride gas was bubbled through it. Solvent was then removed under vacuum, leaving a gray oil, which was triturated with denatured alcohol and seeded with an authentic sample of the desired product to obtain white crystals, which were washed with diethyl ether and recrystallized from dichloromethane/ethanol to obtain 1.86 g. of the desired product, m.p. 235°-236° C.

EXAMPLE 14

6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

A 3 g. portion of 4-(2-piperidinoethoxy)-benzoic acid, hydrochloride, was combined with 20 ml. of 1,2-dichloroethane and 2 drops of dimethylformamide at −20° C., and 4 ml. of phosgene was added. The mixture was stirred for 90 minutes while the temperature was slowly raised to reflux, and then for 30 minutes at reflux. An additional 80 ml. of 1,2-dichloroethane was added, and then 2.7 g. of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene. An 8.68 g. portion of aluminum chloride was added, and the mixture was stirred for 3 hours. An additional 2.66 g. of aluminum chloride was added, and the mixture was stirred for 16 hours more. The mixture was poured into a large amount of 1/1 dichloromethane/dilute aqueous hydrochloric acid. Additional dichloromethane containing a little methanol was added until distinct layers separated. The water layer was extracted several times with dichloromethane containing a little methanol, and the organic layers were combined and washed with water and with aqueous sodium chloride. The organic layer was then filtered and evaporated to an oil, which was dissolved in dichloromethane and a little methanol, and extracted with about 20 ml. of 5% aqueous sodium hydroxide, and then with water, aqueous ammonium chloride and water. The organic layer was then evaporated to about 4 g. of oil, which was dissolved in acetone. Diethyl ether was added, and impurities precipitated and were filtered out. The filtrate was evaporated to about 3.4 g. of foam, which was purified by preparative high-pressure liquid phase chromatography on silica gel, eluting with 1.5% methanol in chloroform. The product-containing fractions were combined and evaporated to obtain the desired product as 1.88 g. of yellow oil; m/e 501.198 by electron impact high resolution mass spectrometry; absorption maximum at 1650 on the infrared spectrum in chloroform; λ_{max} (ϵ): 296 (32,500) on the ultraviolet spectrum in ethanol.

The following example shows a preferred synthesis of a preferred salt.

EXAMPLE 15

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

Five hundred mg. of the product of Example 3 was dissolved in 20 ml. of tetrahydrofuran, and the solution was dried over 4A molecular sieves. Hydrogen chloride gas was then bubbled through the solution, and a pale yellow solid precipitated. The solid product was collected by filtration, washed with diethyl ether and vacuum dried at ambient temperature to obtain 524 mg. of the desired product, m.p. 221°-224° C. The ultraviolet spectrum in ethanol showed λ_{max} (ϵ) 222 nm. (29,000), 287 nm. (28,000).

nmr (100 mHz, dmso-d_6): δ1.76 (6H, m, $N(CH_2\underline{CH_2})_2\underline{CH_2}$); 3.40 (6H, m, $N(\underline{CH_2}CH_2)_2CH_2$ and $OCH_2\underline{CH_2}N$); 4.42 (2H, m, $OCH_2\underline{CH_2}N$); 6.66 (2H, d, J=9 Hz, aromatic o to OH); 6.85 (1H, q, J=9 Hz and J=2 Hz, H5 of benzothiophene ring); 6.95 (2H, d, J=9 Hz, aromatic o to OCH_2CH_2N); 7.15 (2H, d, J=9 Hz, aromatic m to OH); 7.23 (1H, d, J=9 Hz, H4 of benzothiophene ring); 7.34 (1H, d, J=2 Hz, H7 of benzothiophene ring); 7.68 (2H, d, J=9 Hz, aromatic o to CO); 9.76 (2H, broad s, OH); 10.40 (1H, broad s, NH).

EXAMPLE 16

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

A mixture of 1.5 g. of 4-(2-piperidinoethoxy)-benzoic acid, hydrochloride, 20 ml. of chlorobenzene, 3 ml. of thionyl chloride and 2 drops of dimethylformamide was stirred at 75°-79° for 2 hours, to prepare the corresponding acid chloride. Vacuum was then applied, and the temperature dropped to 65°. Distillation was continued until the pot temperature was 90°. Twenty ml. of additional chlorobenzene was added, and the mixture was redistilled to a pot temperature of 90°, and was then cooled. To the mixture was added 15 ml. of dichloromethane, 1.35 g. of 6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene, 5 g. of aluminum chloride and 15 ml. of additional dichloromethane. The mixture was stirred at 27°-29° for 90 minutes, and then 1.6 ml. of ethanethiol was added. The mixture was stirred with cooling to maintain it at or below 35°. After 30 minutes, the mixture was worked up as described in Example 8 above, except that only 18 ml. of tetrahydrofuran and of water were used, to obtain 2.6 g. of the crude desired product, m.p. 217°, which was found to be substantially identical to the product of Example 8 by nmr and thin layer chromatography.

EXAMPLE 17

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

The process of Example 16 was followed once more, except that 1.8 ml. of ethanethiol was used, and a different work up procedure was applied as follows. The mixture was stirred for 30 minutes after the addition of the ethanethiol, and to it was added 4 ml. of methanol, producing vigorous evolution of gas and a temperature rise, with cooling, to 30° C. Six ml. more methanol was added, followed by 5 ml. of 20% hydrochloric acid and 18 ml. of water, while the mixture was held at about 25° C. The mixture was stirred for about 30 minutes, and

was then filtered. The solids were washed twice with 25 ml. portions of water and twice with 25 ml. portions of diethyl ether. The solids were dried, and found to be 2.55 g. of the crude desired product, m.p. 219° C. dec., essentially identical to the product of Example 8 by nmr and thin layer chromatography.

EXAMPLE 18

Purification of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

Two hundred g. of crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride, typical of the product of Example 16 above, was added to 4400 ml. of methanol and 60 ml. of deionized water in a 5-liter flask. The slurry was heated to reflux, whereupon most of the crude product went into solution. The remaining solid was removed by filtration under vacuum, using a filter aid pad. A distillation head was then attached to the flask, and solvent was distilled off until the volume of the remaining solution was about 1800 ml. The heating mantle was then turned off, and the solution was cooled very slowly overnight, with constant stirring. The crystalline product was then collected by vacuum filtration, and the flask was washed out with filtrate to obtain all of the product. The crystals were washed on the filter with two 100 ml. portions of cold (below 0° C.) methanol, and the washed product was dried at 60° C. under vacuum to obtain 140 g. of dried product.

The product was slurried in 3000 ml. of methanol and 42 ml. of water, heated to reflux and cooled very slowly. The product was filtered and dried as above to obtain 121 g. of highly purified product, m.p. 259°-260° C.

EXAMPLE 19

6-Methoxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride

A mixture of 9 g. of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, 100 ml. of chlorobenzene, 15 ml. of thionyl chloride and 5 drops of dimethylformamide was stirred at 75°-79° C. for 2 hours, to prepare the corresponding acid chloride. Excess thionyl chloride and part of the chlorobenzene was removed by distillation under vacuum to a maximum pot temperature of 85° C. Fifty ml. of additional chlorobenzene was added, and the distillation of 85° C. was repeated. The residue was then dissolved in 100 ml. of dichloromethane, and to it was added 8.1 g. of 6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene, 50 ml. of additional dichloromethane and 30 g. of aluminum chloride. The mixture ws stirred at 27°-29° C. for 90 minutes, and was then cooled. To the mixture was added 108 ml. of tetrahydrofuran, followed by 30 ml. of 20% aqueous hydrochloric acid and 108 ml. of water. The water phase was then removed, and was extracted with 50 ml. of dichloromethane. The organic layers were combined, and extracted with 90 ml. of water. The organic portion was then dried over sodium sulfate, and evaporated to a solid under vacuum. About 31 g. of wet crude product was obtained.

The crude product was slurried in 200 ml. of hot chlorobenzene, and the slurry was cooled in an ice bath and filtered at 5° C. The solids were washed with 30 ml. of chlorobenzene, and dried under vacuum to obtain 10.6 g. of the desired product. About 1.8 g. of additional product was obtained by chromatography of the filtrate on silica gel, eluting with methanol. The melting point of the main product was 216° C. dec. Its identity was confirmed by 90 mHz nmr in $CDCl_3$, which showed the following characteristic features.

δ1.6 (m, 2H, $N(CH_2CH_2)_2CH_2$); 2.0 (m, 4H, $N(CH_2CH_2)_2$); 3.1 (m, 4H, $N(CH_2CH_2)_2$); 3.3 (m, 2H, $CH_2N(CH_2)_5$); 3.7 and 3.9 (s, 3H, OCH_3); 4.5 (n, 2H, OCH_2) 6.7-7.8 (m, 11H, aromatic).

The following reports of biological tests illustrate the usefulness of the compounds of this invention. The compound used in many of the tests reported below was the dihydroxy compound, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene.

The first test reported below is used to determine the estrogenic potency of compounds. It is well known that many compounds having antiestrogenic activity also, typically, have estrogenic activity. As has been explained, estrogenic activity is a liability in an antiestrogen, and thus it is important to identify antiestrogens having a minimum amount of estrogenic activity.

Test 1

Estrogenic Response Test

This test was conducted with immature 40-45 g. female rats, immature 11-13 g. mice, and adult ovariectomized mice. The rats were tested in groups of six, and mice in groups of ten. All of the laboratory animals were from standardized strains and were equilibrated to the laboratory before the test started. Each test was begun by administering the test compound daily for three days, as a subcutaneous injection or by oral gavage, as indicated below in the reports of individual experiments. Untreated control animals were included in each experiment, along with animals to which estradiol was administered subcutaneously. The estradiol-treated animals provided positive controls, showing the physiological effect of a potent estrogen on the individual group of animals used in the experiment. The usual dose of estradiol was 0.1 mcg./day, which dose approximates the physiological level.

The test animals were treated for three days and sacrificed on the fourth day, and the uteri were removed, freed of extraneous tissue, and blotted with paper towels. The uteri were weighed to the nearest 0.1 mg.

The tables below report the results of representative experiments. The doses of estradiol and of the compound of this invention are given as the total of the three daily doses. The uterine weights are given, in mg., as the means of all of the organ weights of the animals in a group. Compounds are referred to by their example numbers above.

TABLE I

Treatment	Uterine Weight
Immature rats	
Experiment A	
Control	23.0 mg.
Estradiol, 0.3 mcg., s.c.	74.6
Example 3, 3 mcg., s.c.	47.7
Example 3, 30 mcg., s.c.	38.4
Example 3, 300 mcg., s.c.	35.9
Example 3, 3 mg., s.c.	33.9
Experiment B	
Control	23.8 mg.
Estradiol, 0.3 mcg., s.c.	56.8
Example 3, 3 mcg., oral	34.5
Example 3, 30 mcg., oral	34.4

TABLE I-continued

Treatment	Uterine Weight
Example 3, 300 mcg., oral	33.2
Example 3, 3 mcg., oral	34.4
Experiment C	
Control	25.4 mg.
Estradiol, 0.3 mcg., s.c.	63.1
Example 9, 3 mg., s.c.	31.3
Example 10, 3 mg., s.c.	30.8
Example 11, 3 mg., s.c.	37.1
Example 12, 3 mg., s.c.	35.8
Example 13, 3 mg., s.c.	39.6
Example 14, 3 mg., s.c.	35.1
Immature mice	
Experiment D	
Control	10.6 mg.
Estradiol, 0.03 mcg., s.c.	33.3
Estradiol, 0.09 mcg., s.c.	48.2
Estradiol, 0.3 mcg., s.c.	50.3
Example 3, 0.03 mcg., s.c.	19.0
Example 3, 0.3 mcg., s.c.	19.3
Example 3, 3 mcg., s.c.	22.9
Example 3, 30 mcg., s.c.	23.9
Example 3, 300 mcg., s.c.	19.3
Example 3, 3 mg., s.c.	14.6
Mature ovariectomized mice	
Experiment E	
Control	12.3 mg.
Estradiol, 0.03 mcg., s.c.	25.8
Estradiol, 0.1 mcg., s.c.	44.2
Estradiol, 0.3 mcg., s.c.	65.9
Example 3, 0.3 mcg., s.c.	18.2
Example 3, 3 mcg., s.c.	25.6
Example 3, 30 mcg., s.c.	26.2
Example 3, 300 mcg., s.c.	24.8
Example 3, 3 mg., s.c.	23.1

The experiments reported next below are antiestrogenic response experiments, in which the test animals were treated both with estradiol and with the same compound of this invention used in the experiments above. The purpose of the experiments below was to determine the extent to which the estrogenic response of estradiol could be inhibited by treatment with compounds of this invention.

Test 2

Antiestrogenic Tests

The same standardized types of laboratory animals which were used in the experiments described above were also used in these experiments. A compound of this invention, identified below by its example number, was administered, orally or subcutaneously, together with subcutaneous estradiol. Untreated control animals were used in each experiment. The dose of estradiol in each experiment is given in the first line of each table, followed by the doses of the compound of this invention which were given along with the established dose of estradiol to produce inhibition of the estrogenic effect of the estradiol. The dosage and sacrifice schedule, and the method of determining uterine weights and reporting data, were the same as the methods described above under Test 1.

TABLE II

Treatment	Uterine weight
Mature ovariectomized mice	
Experiment A	
Control	12.3 mg.
Estradiol, 0.3 mcg., s.c.	65.9
Example 3, 0.3 mcg., s.c.	54.9
Example 3, 3 mcg., s.c.	48.7

TABLE II-continued

Treatment	Uterine weight
Example 3, 30 mcg., s.c.	31.1
Example 3, 300 mcg., s.c.	22.1
Example 3, 3 mg., s.c.	21.3
Immature mice	
Experiment B	
Control	10.6 mg.
Estradiol, 0.3 mcg., s.c.	50.3
Example 3, 0.03 mcg., s.c.	41.3
Example 3, 0.3 mcg., s.c.	40.6
Example 3, 3 mcg., s.c.	26.5
Example 3, 30 mcg., s.c.	18.9
Example 3, 300 mcg., s.c.	14.6
Example 3, 3 mg., s.c.	13.9
Immature rats	
Experiment C	
Control	23.8 mg.
Estradiol, 0.3 mcg., s.c.	56.8
Example 3, 3 mcg., oral	55.0
Example 3, 30 mcg., oral	46.7
Example 3, 300 mcg., oral	31.3
Example 3, 3 mg., oral	30.6
Experiment D	
Control	21.1 mg.
Estradiol, 0.3 mcg., s.c.	71.5
Example 3, 3 mcg., s.c.	53.6
Example 3, 30 mcg., s.c.	33.7
Example 3, 300 mcg., s.c.	30.7
Example 3, 3 mg., s.c.	28.0
Experiment E	
Control	30.0 mg.
Estradiol, 0.09 mcg., s.c.	44.9
Example 3, 3 mcg., s.c.	42.5
Example 3, 30 mcg., s.c.	35.8
Example 3, 300 mcg., s.c.	33.7
Example 3, 3 mg., s.c.	31.0
Experiment F	
Control	30.0 mg.
Estradiol, 0.15 mcg., s.c.	50.9
Example 3, 3 mcg., s.c.	49.4
Example 3, 30 mcg., s.c.	40.9
Example 3, 300 mcg., s.c.	36.5
Example 3, 3 mg., s.c.	36.2
Experiment G	
Control	24.8
Estradiol, 3 mcg., s.c.	84.4
Example 3, 3 mcg., s.c.	71.9
Example 3, 30 mcg., s.c.	42.2
Example 3, 300 mcg., s.c.	33.7
Example 3, 3 mg., s.c.	30.2
Experiment H	
Control	24.8 mg.
Estradiol, 30 mcg., s.c.	113.2
Example 3, 3 mcg., s.c.	92.7
Example 3, 30 mcg., s.c.	60.2
Example 3, 300 mcg., s.c.	48.9
Example 3, 3 mg., s.c.	33.1
Experiment I	
Control	25.4 mg.
Estradiol, 0.3 mcg., s.c.	63.1
Example 9, 3 mg., s.c.	38.1
Example 10, 3 mg., s.c.	32.2
Example 11, 3 mg., s.c.	40.0
Example 12, 3 mg., s.c.	31.8
Example 13, 3 mg., s.c.	41.1
Example 14, 3 mg., s.c.	37.5

The following test was carried out to determine if the compounds of this invention could reverse an estrogenic response, when administration of the compound was started after the estrogenic response had become established.

Test 3

Regression Tests

The same basic scheme of Tests 1 and 2 was followed in this experiment, except that the administration of estradiol was begun before the administration of the compound of Example 3 above. The test animals were immature rats, and all administrations were by subcutaneous injection.

The mean uterine weight of the untreated control animals was 20.9 mg.

Estradiol alone was administered to groups of animals at the rate of 0.1 mcg./day for three, four, six, and eight days, and each group of animals was sacrificed on the day after the last treatment day. The mean uterine weights of these groups of animals, respectively, were 97.9, 97.3, 119.9 and 112.3 mg.

One group of compound-treated animals was given estradiol at 0.1 mcg./day for three days, and was given 0.1 mcg. of estradiol and 1 mg. of the compound of this invention on the fourth day. The animals were sacrificed on the fifth day and their mean uterine weight was 56.4 mg.

Another group of treated animals was given 0.1 mcg. of estradiol per day for three days and was given 0.1 mcg. of estradiol and 1 mg. of the compound of this invention on each of the following three days. The animals were sacrificed on the seventh day and their mean uterine weight was 57.0 mg.

A final group of compound-treated animals was given 0.1 mcg. of estradiol on each of three days, and was then given 0.1 mcg. of estradiol and 1 mg. of the compound of this invention on each of the following five days. They were sacrificed on the ninth day and their mean uterine weight was found to be 50.7 mg.

Another group of control animals was sacrificed on the ninth day of this experiment, since the animals had been growing through the long period of the experiment, and their mean uterine weight was found to be 31.1 mg.

The results of the experiments reported in this test clearly show that the compounds of this invention are capable of reversing an established estrogenic response when the compounds are administered after the response is established.

Additional experiments have been done to determine the ability of the compounds of this invention to bind to the estrogen-receptor, and their rate of dissociation from the receptor, relative to the rate of dissociation of estradiol.

Test 4

Relative Binding Affinity Tests

A group of immature 40–45 g. female laboratory rats of a standardized strain were sacrificed, and their uteri were promptly removed and dissected free of adhering fat and other extraneous tissue. The uteri, which were constantly kept cold, were homogenized in a buffer which contained 10 mM tris(hydroxymethyl)aminomethane, hydrochloride and 1.5 mM ethylenediaminetetraacetic acid at pH 7.4, at a concentration of 1 uterus/ml. The homogenate was then centrifuged for one hour at 100,000×G at 4° C., and the supernatant, containing the cytosol fraction, was retained.

One-half ml. of the cytosol preparation was added to each of a group of tubes which contained 10 nM of 2,4,6,7-^{3}H estradiol, or the labeled estradiol plus log concentrations from 10 to 1000 nM of unlabeled competitor which could be the compound to be tested, that of Example 3, or additional, unlabeled, estradiol. All assays were performed in duplicate, and all assays in a given experimental group were carried out on aliquots from the same pool of cytosol preparation.

Samples were then mixed and incubated at specified temperatures. Each incubation was ended at the specified time by cooling the sample and adding 0.5 ml. of a dextran-coated charcoal suspension containing 10 mM tris(hydroxymethyl)aminomethane, hydrochloride, 1 mM of ethylenediaminetetraacetic acid, 1% of charcoal and 0.1% of dextran at pH 8. The samples were agitated frequently for fifteen minutes at 4° C., and then centrifuged at 800×G at the same temperature for fifteen minutes. The supernatant from the centrifugation contained the cytosol preparation, free of unbound estradiol and estradiol-competitors, which were adsorbed by the charcoal.

Each one-half ml. aliquot of supernatant was transferred to a 20 ml. vial of scintillation solution, and DPM was measured by liquid scintillation spectrometry. The difference between total DPM in control samples containing only labeled estradiol, and that observed in the presence of 1000 nM of unlabeled estradiol was considered to be specific binding. The concentration of unlabeled estradiol on the inhibition curve which corresponded to 50% inhibition of specific binding was determined, as was the concentration on the inhibition curve of the compound of this invention which corresponded to 50% inhibition of specific binding. Relative binding affinity (RBA) was calculated as the concentration of estradiol which gave 50% inhibition, divided by the concentration of the test compound which gave 50% inhibition.

Experiments were carried out at 4°, 15° and 30° C., and for periods of one half hour, one hour and 24 hours in various tests. The table below lists the relative binding affinities which were found in a number of experiments, carried out as described above, at the various conditions listed in the headings of the table.

TABLE III

Experiment	4° C., 1 hour	4° C., 24 hours	15° C., 1 hour	30° C., ½ hour
1	1.6	1.03	0.6	1.2
2	1.7	1.9	1.9	2.3
3	3.7	1.2	1.7	2.5
4	1.1	1.5	1.9	3.8
5	2.7	2.0	1.9	2.0
6	0.8	1.3	0.9	1.9
7	0.6	4.0	2.3	—
8	<0*	1.2	0.8	1.8
9	0.9	0.9	—	1.2
10	1.3	4.2	—	3.2

*In this test, no concentration of the test compound achieved 50% inhibition.

The compounds of this invention have also been tested to determine the facility with which they dissociate from the estrogen receptor.

Test 5

Dissociation Tests

A cytosol preparation was made as described in Test 4, but at a concentration of 2 uteri per ml. One-half ml. aliquots of the cytosol preparation were incubated for one hour at 4° C. with 2,000 nM of the compound of Example 3, or of unlabeled estradiol. After one hour, 0.5 ml. of dextran-coated charcoal suspension was

added, the samples were agitated frequently for fifteen minutes, and were then centrifuged at 800×G at 4° C. for fifteen minutes to remove unbound molecules. One-half ml. aliquots of the treated cytosol preparation were then transferred to two sets of tubes, one containing 10 nM of labeled estradiol and the other containing 1,000 nM of unlabeled estradiol as well as 10 nM of labeled estradiol. Two sets of samples were run for each condition.

The samples were then incubated at specified temperatures and times, and were terminated at the end of the designated times by cooling them in an ice bath and adding 0.5 ml. of the dextran-coated charcoal suspension to each. The samples were agitated and centrifuged, and 0.5 ml. of supernatant from each was added to scintillation fluid for determination of DPM as described under Test 4. The DPM observed in samples containing 1,000 nM of unlabeled estradiol was subtracted from the readings for corresponding samples with labeled estradiol only, to determine specific binding for each condition. The percent difference in specifically bound DPM between the cytosol exposed to the compound of this invention, or of unlabeled estradiol, and unexposed controls, at each time point was determined and expressed as relative percent bound for the compound and for estradiol.

TABLE IV

Experiment		1 min.	5 min.	15 min.	30 min.	1 hour	2 hours
			30° C.				
A	Compound	61%	70%	50%	26%	3%	19%
	Estradiol	63%	45%	46%	47%	24%	43%
B	Compound	76%	71%	55%	48%	38%	40%
	Estradiol	87%	64%	37%	33%	15%	14%
C	Compound	50%	54%	34%	24%	20%	24%
	Estradiol	62%	48%	24%	18%	6%	1%
D	Compound	52%	58%	43%	38%	33%	20%
	Estradiol	64%	54%	18%	25%	21%	24%
E	Compound	67%	57%	43%	20%	16%	26%
	Estradiol	67%	38%	41%	23%	10%	22%
F	Compound	53%	67%	68%	57%	55%	53%
	Estradiol	51%	45%	35%	34%	24%	5%
			4° C.				
G	Compound	76%	72%	58%	76%	64%	65%
	Estradiol	81%	77%	67%	66%	57%	52%
H	Compound	65%	65%	42%	71%	77%	0
	Estradiol	73%	76%	63%	57%	61%	63%
I	Compound	67%	68%	93%	80%	77%	62%
	Estradiol	51%	80%	85%	76%	93%	77%
J	Compound	43%	9%	93%	77%	100%	74%
	Estradiol	26%	71%	85%	70%	74%	68%
K	Compound	37%	36%	60%	55%	60%	64%
	Estradiol	68%	48%	52%	51%	35%	46%
L	Compound	58%	54%	53%	72%	57%	58%
	Estradiol	58%	66%	48%	65%	60%	58%

The above data clearly show that the representative compound of this invention which was tested has a high affinity for the estrogen receptor, and dissociates from it less readily than does estradiol.

The effect of a representative compound of this invention against mammary tumors in the rat has been determined in tests carried out as follows.

Test 6

Tests Against DMBA-Induced Tumors

Mammary tumors were induced in adult female virgin rats by a single 20-mg. oral dose of 7,12-dimethylbenzanthracene. Within about six weeks, visible and palpable tumors were present in the mammary tissue of the rats, and the rats were allocated into treatment and control groups in such a way that each group contained animals having approximately the same size and number of tumors. The size of the tumors was estimated by measuring their cross-sectional area.

At the end of the test, the animals were ovariectomized, all treatments were stopped, and the animals were observed to determine if the tumors regressed, due to the lack of estrogen in the system. Most of the DMBA-induced tumors evidently were estrogen-dependent, because most of them immediately regressed upon ovariectomy. Exceptions, where the tumors did not regress after ovariectomy, are foot-noted in the reports of individual experiments below.

Experiment A

In this experiment, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene was administered orally to each animal for eight weeks. In the first two-week period, the animals were given 0.1 mg./kg./day, which dose was increased to 5, 10 and 20 mg./kg./day in successive two-week intervals. The control animals were handled each day and given an oral dose of 0.5 ml. of corn oil, as a blank. At the end of the eight-week period, the tumors of the control animals had total cross-sectional areas which averaged 1957 square millimeters, and ranged from 512 square millimeters to 4030 square millimeters.

The animals which had been treated with the compound of this invention, in contrast, had an average total cross-sectional area of tumor of 345 square millimeters, ranging from complete regression to one animal having 1550 sq. mm. total cross-sectional area. The tumors of this animal, however, were not estrogen-dependent, and did not regress when the animal was ovariectomized. One animal in the compound-treated group could not be evaluated, because its tumors had changed to an impalpable form, or, perhaps, had completely regressed but had left some abnormalities in the tissue after its regression.

Experiment B

In this experiment, the same compound was administered at 20 mg./kg./day, orally, for four weeks. In other respects, the test was run in the same way as that of Experiment A above. At the end of the four weeks, the average total tumor area of the control animals was 487 square millimeters, ranging from 178 to 886 square millimeters. The tumors of one of the compound-treated animals had completely regressed, with no palpable tumor present at the end of the four-week period; the other five animals had tumor areas from 16 to 668 square millimeters; the average total area of the treated animals was 152 square millimeters. The large tumor of the compound-treated animal having an area of 668 square millimeters was found to shrink after ovariectomy, but its growth had been checked, and it had not significantly grown, since the second week of the experiment. Thus, it was apparently a partially estrogen-dependent tumor.

Experiment C

This experiment was also carried out for four weeks, and two groups of treated animals were used. One group of animals received 20 mg./kg./day of the same compound used in Experiments A and B, and the other received 40 mg./kg./day. The animals were not ovariectomized at the end of the experiment.

At the end of the four weeks, the control animals, of which there were ten, were found to have an average total tumor area of 958 square millimeters, ranging from 168 to 2,094 square millimeters. The average cross-sectional tumor area of the animals which received the low dose of the compound of this invention was 441 square millimeters, with a range from no tumors present to 1907 square millimeters. The animals which received the high dose of the compound had even smaller tumors, averaging 304 square millimeters, with a range from 116 to 758 square millimeters.

Experiment D

This experiment was followed for five weeks. The treated animals received 1 mg./kg. per day of 6-methoxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, hydrochloride, as a subcutaneous injection in corn oil. The animals were not ovariectomized at the end of the experiment.

At the end of four weeks, the seven control animals had an average total tumor area of 1,446 square millimeters, ranging from 592 to 2,400. At the end of five weeks, the tumors of two of the control animals had burst and were unmeasurable; the tumors of the other five controls averaged 1,487 square millimeters in total area, ranging from 966 to 2,123.

The tumors of three of the eight treated animals had completely regressed by the fourth week of the test; the average total tumor area of the treated group was 692 square millimeters. If one animal having a tumor area of 3764 sq. mm. is ignored, the average tumor area of the other seven is 254 sq. mm.

At the fifth week of the test, the largest tumors of the treated animal having the largest total at four weeks had burst and were unmeasurable. The other seven treated animals averaged 398 square millimeters, ranging from the three completely regressed animals to one with a single 1974 sq. mm. tumor.

Test 7

Anti-Androgen Tests

The antiandrogenic property of the compounds was evaluated in the following tests, in which the compound of Example 3 was used again.

Experiment A

The animals used in this test were adult male rats having a body weight which averaged about 330 g. when the experiment ended. All of the animals to be used in the experiment were castrated by the scrotal route, and were held untreated for 3 days. On the fourth day, subcutaneous administration of 0.1 mg./day of an exogenous androgen, testosterone propionate, was begun, and was continued for seven consecutive days. An untreated control group of animals received injections of 0.1 ml./day of corn oil as a blank treatment. The compound of this invention was administered orally or subcutaneously to the treated animals in 0.1 ml. of corn oil, at the same time that the androgen was administered. The animals were sacrificed 24 hours after the last injection of testosterone propionate, the ventral prostate glands were removed and weighed, and the mean of the weights of each treatment group was reported. The table below reports the mean weights resulting from administration of various doses of the compound along with androgen.

Each treatment group of animals in this experiment consisted of seven to nine animals, except for the untreated control group, which contained twelve animals. The results of the experiment were as follows.

Treatment	Mean Prostate Weight
Untreated control	40 mg.
Androgen only	309
1 mg./day compound, S.C.	201
0.1 mg./day compound, S.C.	235
0.01 mg./day compound, S.C.	253
1 mg./day compound, oral	242
0.1 mg./day compound, oral	267
0.01 mg./day compound, oral	192

Experiment B

This experiment was carried out in the same manner as Experiment A above, except that the test animals were immature male rats, weighing about 120 g. each at sacrifice. Each treatment group consisted of six or seven animals. All treatments in this experiment were administered by subcutaneous injection. The amount of the androgen administered was only 20 mcg./day because of the small size of the animals.

Treatment	Mean Prostate Weight
Untreated control	12.6 mg.
Androgen only	48.7
5 mg./kg./day compound	36.6
0.5 mg./kg./day compound	33.8*

*One animal in this group had a surprisingly large prostate weighing 54 mg. If this animal is excluded from the group, the average weight is 30.5.

Experiment C

This experiment was also conducted in immature rats having average body weight of about 115 g. when the experiment ended. In other respects, the experiment was as described under Experiment B above. The treatment groups consisted of ten animals each, except for the androgen only group, of 16 animals, and the 5 mg./kg. group, of nine animals.

Treatment	Mean Prostate Weight
Untreated control	11.4 mg.
Androgen only	43.5
5 mg./kg./day compound	29.0
0.5 mg./kg./day compound	31.1
0.05 mg./kg./day compound	34.0

The experiments above show clearly that the representative compound of this invention in the tests inhibited a large part of the abnormal prostate growth caused by the administration of exogenous androgen, and therefore that the compounds of this invention are of interest and importance in the treatment of androgen-dependent abnormal conditions, especially benign prostatic hypertrophy and prostatic cancer.

As has been stated, this invention provides a method of alleviating a pathological condition of an endocrine target organ, which condition is dependent or partially dependent on an estrogen or on an androgen, which comprises administering an effective dose of a compound as described above to a subject suffering from

such a condition or at risk of suffering from such a condition.

The preferred compounds of this invention are 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene and its physiologically acceptable salts, especially the hydrochloride. Other preferred compounds include 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, 6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidnoethoxy)benzoyl]benzo[b]thiophene, 6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene and 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, and their physiologically acceptable salts, especially the hydrochlorides.

The effect of the compounds of this invention is described as alleviating the pathological conditions, to indicate that complete cure of the conditions cannot always be expected, but that use of an effective dose of the compounds will benefit the subject by causing at least some regression of the condition. When the compounds are used preventively, as in a subject who has suffered from an occurrence of mammary fibrocystic disease and is at risk of further occurrences, the compounds will prevent such occurrences or, at least, lessen or delay the severity of their effects.

Use in human subjects is preferred.

The compounds of this invention are improved antiestrogens, compared to earlier compounds, because they have a higher ability to inhibit estrogenic response and have less inherent estrogenicity than the earlier compounds. The compounds of this invention, accordingly, give a greater antiestrogenic effect for a given dose of compound, inhibit more effectively at the optimum dose, and contribute less incidental estrogenic response than any prior-known antiestrogen. Their antiandrogenic properties, combined with their antiestrogenic properties, make the compounds of this invention still more unique.

It is believed that the present compounds are relatively quite free of a histological side-effect common to earlier anti-estrogens. Tamoxifen, for example, causes abnormal growth of uterine epithelial cells. Preliminary studies indicate that the present compounds either cause no abnormality of epithelial cells of the uterus, or cause only extremely slight abnormal growth.

The exact mechanism of an antiestrogen in treating mammary cancer is not known. It is believed, however, that the antiestrogen, circulating in the body, competes with endogenous estrogens for estrogen receptor sites in the cancer. To be effective, the antiestrogen must find and bind to receptor sites, and prevent estradiol from occupying them. Clearly, if the antiestrogen has inherent estrogenicity of its own, it is likely to enable the cancer to grow just as if the cancer had absorbed endogenous estrogen.

The biological tests reported above show the low estrogenicity, high antiestrogenicity and strong affinity for estrogen receptor sites of the compounds of this invention.

Accordingly, a most important embodiment of the present invention is a method of alleviating mammary cancers which comprises administering a compound of this invention at an effective rate to a patient suffering from or at risk of such a cancer.

The antiestrogens of this invention are believed to have other biological effects as well. Antiestrogens play a role in the treatment of fibrocystic disease of the mammary glands, which role is as yet less well defined than is their use in the treatment of mammary cancers. It is believed, however, that fibrocystic disease, which manifests itself in benign lumps or growths in mammary tissue, is estrogen-dependent. It has been established that the administration of antiestrogens to patients who have or who have shown a tendency toward fibrocystic disease can alleviate it by both causing the regression of the symptoms of it, and preventing its recurrence. Accordingly, the administration of a compound of this invention to a patient having or at risk of fibrocystic disease to alleviate the disease, is an important embodiment of the invention.

Further, the tests presented above illustrate that the compounds of this invention have an important antiandrogenic effect on the prostate gland. Benign prostatic hypertrophy is a very common and distressing condition, manifested by abnormal growth of the prostate gland. An effective drug for the control of this condition has long been sought. The tests reported above show that compounds of this invention have a strong effect on androgen stimulation and maintenance of the size of the prostate gland. Accordingly, it is expected that the compounds of this invention can be administered to males suffering from or at risk of benign prostatic hypertrophy to alleviate the condition. The method of alleviating benign prostatic hypertrophy by administering an effective dose of a compound of this invention is, accordingly, an important embodiment of the invention.

Similarly, use of anti-androgens in patients suffering from prostatic cancer is known to interrupt the progression of the cancer, because prostatic cancer is dependent upon androgen for its growth, and the anti-androgenic compounds of this invention interrupt the course of the disease by preventing the cancer from utilizing endogenous androgen in the patient's system. The exact mode of action of the compounds as anti-androgens has not been elucidated, but the in vivo tests reported above show clearly that the compounds are, indeed, anti-androgens. Accordingly, the use of the compounds of this invention to alleviate prostatic cancer is another important embodiment of the invention.

The tests which have been applied to a representative compound of this invention were carried out in standard laboratory animals, as described above. The tests which have been applied to the compounds are believed to be clearly predictive of beneficial effects in humans, based on the effects in laboratory animals.

The dose of a compound of this invention to be administered to a human is rather widely variable. It should be noted that it may be necessary to adjust the dose of a compound when it is administered in the form of a salt, such as a laurate, the salt-forming moiety of which has an appreciable molecular weight. The general range of effective administration rates of the compounds is from about 0.05 mg./kg./day to about 50 mg./kg./day. A preferred rate range is from about 0.1 mg./kg./day to about 10 mg./kg./day, and the most highly preferred range is from about 0.1 mg./kg./day to about 5 mg./kg./day. Of course, it is often practical to administer the daily dose of a compound in portions, at various hours of the day.

The route of administration of the compounds of this invention is not critical. The compounds are known to be absorbed from th alimentary tract, and so it is usually preferred to administer a compound orally for reasons of convenience. However, the compounds may equally

effectively be administered percutaneously, or as suppositories for absorption by the rectum, if desired in a given instance.

The compounds of this invention are usually administered as pharmaceutical compositions which are important and novel embodiments of the invention because of the presence of the compounds. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions. Compositions are formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be a single tablet or capsule or a convenient volume of a liquid. In general, compositions contain from about 0.000006% of compound, depending on the desired dose and the type of composition to be used.

The activity of the compounds does not depend on the compositions in which they are administered or on the concentration of the composition. Thus, the compositions are chosen and formulated solely for convenience and economy.

Any of the compounds may be readily formulated as tablets, capsules and the like; it is preferable to prepare solutions from water-soluble salts, such as the hydrochloride salt.

In general, all of the compositions are prepared according to methods usual in pharmaceutical chemistry. Some discussion will be provided, followed by a group of typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established in the art.

When it is desired to administer a compound as a suppository, the typical bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

The effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly-soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The techique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Even parenteral preparations may be made long-acting, by dissolving or suspending the compound in oily or emulsified vehicles which allow it to disperse only slowly into the serum.

The following typical formulae are provided further to assist the formulations chemist.

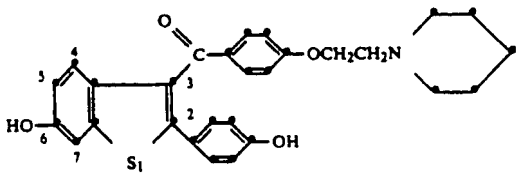
Capsules	
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride	3 mg.
Microcrystalline cellulose	400
Pregelatinized starch	95
Silicone fluid	2
6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, acetate	150 mg.
Pregelatinized starch	106
Starch	52
Silicone fluid	1.6
6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride	300 mg.
Pregelatinized starch	200
Solutions	
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride	3 mg.
Purified water	5 cc.
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, hydrochloride	20 mg.
Purified water	5 cc.
Tablets	
6-cyclopentoxy-2-(4-cyclopentoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene	5 mg.
Microcrystalline cellulose	240
Starch	45
Stearic acid	6
Magnesium stearate	3
Colloidal silicon dioxide	1
6-benzyloxy-2-(4-benzyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene, benzoate	150 mg.
Microcrystalline cellulose	128
Lactose	25
Pregelatinized starch	10
Stearic acid	8
Magnesium stearate	3
Colloidal silicon dioxide	2
6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene	250 mg.
Calcium phosphate	58
Lactose	54
Microcrystalline cellulose	31

-continued

Starch	5
Stearic acid	2
Magnesium stearate	1

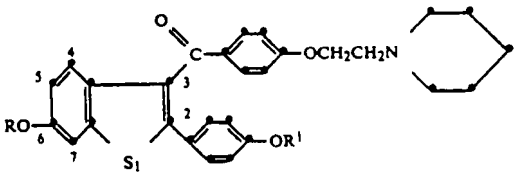
I claim:

1. A compound of the formula



a physiologically acceptable ester or ether thereof, or a physiologically acceptable acid addition salt thereof.

2. A compound of claim 1 of the formula



wherein R and R^1 independently are hydrogen, $-COR^2$ or R^3;

R^2 is hydrogen, C_1–C_{14} alkyl, C_1–C_3 chloroalkyl, C_1–C_3 fluoroalkyl, C_5–C_7 cycloalkyl, C_1–C_4 alkoxy, phenyl, or phenyl mono- or disubstituted with C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl;

R^3 is C_1–C_4 alkyl, C_5–C_7 cycloalkyl or benzyl; or a physiologically acceptable acid addition salt thereof.

3. The compound of claim 2 which is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

4. A compound of claim 2 wherein R and R^1 are the same, and are a group other than hydrogen.

5. A compound of claim 2 wherein one of R and R^1 is hydrogen.

6. A compound of claim 2 wherein one or both of R and R^1 is $-COR^2$.

7. A compound of claim 2 wherein one or both of R and R^1 is R^3.

8. A compound of any one of claims 2, 4 or 6 wherein R^2 is C_1–C_{14} alkyl.

9. A compound of any one of claims 2, 4 or 6 wherein R^2 is C_1–C_3 chloroalkyl or C_1–C_3 fluoroalkyl.

10. A compound of any one of claims 2, 4 or 6 wherein R^2 is C_5–C_7 cycloalkyl.

11. A compound of any one of claims 2, 4 or 6 wherein R^2 is C_1–C_4 alkoxy.

12. A compound of any one of claims 2, 4 or 6 wherein R^2 is phenyl.

13. A compound of any one of claims 2, 4 or 6 wherein R^2 is substituted phenyl.

14. A compound of any one of claims 2, 4, 5 or 7 wherein R^3 is C_1–C_4 alkyl.

15. A compound of any one of claims 2, 4, 5 or 7 wherein R^3 is C_5–C_7 cycloalkyl.

16. A compound of any one of claims 2, 4, 5 or 7 wherein R^3 is benzyl.

17. A compound of any one of claims 1–7 which is a free base.

18. A compound of any one of claims 1–7 which is a physiologically acceptable acid addition salt.

19. A compound of any one of claims 1–7 which is a hydrochloride.

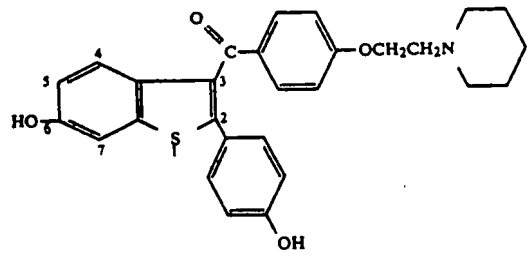
20. The compound of claim 1 which is 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

21. The compound of claim 1 which is 6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

22. The compound of claim 1 which is 6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

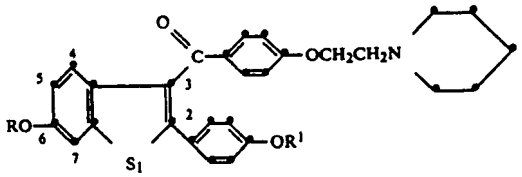
23. The compound of claim 1 which is 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

24. An antiestrogenic and antiandrogenic pharmaceutical composition comprising a pharmaceutically acceptable diluent and an effective amount of a compound of the formula



a physiologically acceptable ester or ether thereof, or a physiologically acceptable acid addition salt thereof.

25. A composition of claim 24 wherein the compound is of the formula



wherein R and R^1 independently are hydrogen, $-COR^2$ or R^3;

R^2 is hydrogen, C_1–C_{14} alkyl, C_1–C_3 chloroalkyl, C_1–C_3 fluoroalkyl, C_5–C_7 cycloalkyl, C_1–C_4 alkoxy, phenyl, or phenyl mono- or disubstituted with C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl;

R^3 is C_1–C_4 alkyl, C_5–C_7 cycloalkyl or benzyl; or a physiologically acceptable acid addition salt thereof.

26. A composition of claim 25 wherein the compound is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoe-

thoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

27. A composition of claim 26 wherein the compound is the hydrochloride.

28. A composition of claim 25 wherein the compound is a compound wherein R and R^1 are the same, and are a group other than hydrogen.

29. A composition of claim 28 wherein the compound is a compound wherein R and R^1 are —COR^2.

30. A composition of claim 29 wherein the compound is a compound wherein R^2 is C_1–C_{14} alkyl.

31. A composition of claim 30 wherein the compound is 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

32. A composition of claim 29 wherein the compound is a compound wherein R^2 is phenyl.

33. A composition of claim 32 wherein the compound is 6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

34. A composition of claim 29 wherein the compound is a compound wherein R^2 is C_1–C_4 alkoxy.

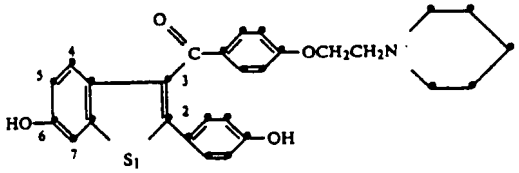
35. A composition of claim 34 wherein the compound is 6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

36. A composition of claim 28 wherein R and R^1 and R^3.

37. A composition of claim 36 wherein the compound is 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

38. A composition of claim 25 wherein the compound is a compound wherein one of R and R^1 is hydrogen.

39. A method of alleviating a pathological condition of an endocrine target organ, which condition is dependent or partially dependent on an estrogen or on an androgen, which comprises administering to a subject suffering from such a condition an effective dose of a compound of the formula



a physiologically acceptble ester or ether thereof, or a physiologically acceptable acid addition salt thereof.

40. A method of claim 39 wherein the pathological condition is dependent or partially dependent on an estrogen.

41. A method of claim 40 wherein the dose of the compound is from about 0.05 mg./kg./day to about 50 mg./kg./day.

42. A method of claim 41 wherein the target organ is the breast, and the pathological condition is mammary cancer.

43. A method of claim 42 wherein the dose of the compound is from about 0.1 mg./kg./day to about 10 mg./kg./day.

44. A method of claim 41 wherein the target organ is the breast, and the pathological condition is fibrocystic disease.

45. A method of claim 44 wherein the dose of the compound is from about 0.1 mg./kg./day to about 10 mg./kg./day.

46. A method of claim 39 wherein the pathological condition is dependent or partially dependent on an androgen.

47. A method of claim 46 wherein the dose of the compound is from about 0.05 mg./kg./day to about 50 mg./kg./day.

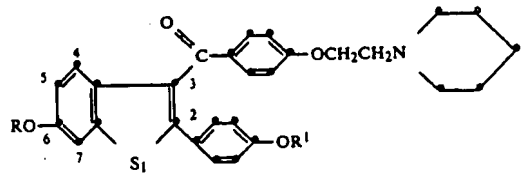
48. A method of claim 47 wherein the target organ is the prostate, and the pathological condition is prostatic cancer.

49. A method of claim 48 wherein the dose of the compound is from about 0.1 mg./kg./day to about 10 mg./kg./day.

50. A method of claim 47 wherein the target organ is the prostate, and the pathological condition is benign prostatic hypertrophy.

51. A method of claim 50 wherein the dose is from about 0.1 mg./kg./day to about 10 mg./kg./day.

52. A method of any one of claims 39–51 wherein the compound is of the formula



wherein R and R^1 independently are hydrogen, —COR^2 or R^3;

R^2 is hydrogen, C_1–C_{14} alkyl, C_1–C_3 chloroalkyl, C_1–C_3 fluoroalkyl, C_5–C_7 cycloalkyl, C_1–C_4 alkoxy, phenyl, or phenyl mono- or disubstituted with C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl;

R^3 is C_1–C_4 alkyl, C_5–C_7 cycloalkyl or benzyl; or a physiologically acceptable acid addition salt thereof.

53. A method of claim 52 wherein the compound is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

54. A method of claim 53 wherein the compound is the hydrochloride.

55. A method of claim 52 wherein the compound is a compound wherein R and R^1 are the same, and are a group other than hydrogen.

56. A method of claim 55 wherein the compound is a compound wherein R and R^1 are —COR^2.

57. A method or claim 56 wherein the compound is 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

58. A method of claim 56 wherein the compound is 6-benzoyloxy-2-(4-benzoyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

59. A method of claim 56 wherein the compound is 6-ethoxycarbonyloxy-2-(4-ethoxycarbonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

60. A method of claim 55 wherein the compound is a compound wherein R and R^1 are R^3.

61. A method of claim 60 wherein the compound is 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, or a physiologically acceptable acid addition salt thereof.

62. A method of claim 52 wherein the compound is a compound wherein one of R and R^1 is hydrogen.

* * * * *

EXHIBIT C

Certificate of Correction for U.S. Patent No. 4,418,068

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,418,068

DATED : November 29, 1983

INVENTOR(S) : Charles D. Jones

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

In the title the word "ANTIANDRUGENIC" should be spelled ---ANTIANDROGENIC---

In Claim 36, the phrase "R and R^1 and R^3" should be replaced with ---R and R^1 are R^3---

Signed and Sealed this

Fifteenth Day of *October 1985*

[SEAL]

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks—Designate

EXHIBIT D

Receipt of Maintenance
Fee Payments Made in
1987, 1991, and 1995

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS [redacted]EMARKS
Washington, D. C. 20231

JOSEPH A. JONES
ELI LILLY & CO., PATENT DIVISION
307 EAST MCCARTY STREET
INDIANAPOLIS, IN 46285

DATE MAILED
01/07/87

01/390

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	[illegible] CDE	[illegible] AMOUNT	SEQ CHANGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT [illegible]
1	4,418,068	170	[illegible]	-	06/331,047	11/29/83	12/16/81	04 [illegible]

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AN[redacted]ARKS
Washington, D. C. 20231

PAYOR NUMBER
000139

ELI LILLY & COMPANY
ATTENTION: PATENT DIVISION/PFEE
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

RECEIVED
APR 8 1991
ELI LILLY AND COMPANY
Patent Division

DATE MAILED
03/29/91

139008

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

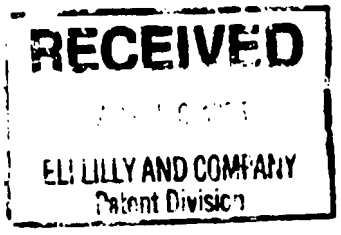
ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,417,046	171	495	----	06/295,419	11/22/83	08/24/81	08	NO	PAID
2	4,417,662	171	495	----	06/260,003	11/29/83	05/04/81	08	NO	PAID
3	4,418,068	171	495	----	06/331,042	11/29/83	12/16/81	[redacted]	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER

75N5/0407

ELI LILLY & COMPANY
ATTENTION: PATENT DIVISION/PFEE
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285



MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l)

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,418,068	185	2900	----	06/331,042	11/29/83	12/16/81	12	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	X-5526A

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

EXHIBIT E

Notice of Claimed Investigational Exemption for a New Drug

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317-276-2000

April 26, 1992

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
12420 Parklawn Drive
Rockville, Maryland 20852

Re: Compound LY139481•HCl (raloxifene hydrochloride)
Serial No. 000

We are submitting herewith an Investigational New Drug application (in 14 volumes) for the new drug product. LY139481•HCl, (raloxifene hydrochloride) for the potential treatment of osteoporosis.

Please refer to a meeting between FDA representatives and Lilly representatives on November 7, 1991. At this meeting Lilly proposed initiation of a Phase 2 clinical trial with raloxifene hydrochloride primarily based upon information which had been submitted previously to the FDA in support of the treatment of breast cancer. In order to adequately carry out the proposed Phase 2 study we believe that a dose range of the new drug product should be evaluated. Accordingly, this letter is accompanied by Form FDA 1571 information supporting a Phase 1 dose ranging study with raloxifene hydrochloride.

Reference is made to the phone conversation (April 21, 1992) between Mr. James Cheever of the FDA and Dr. Paul Gesellchen of Eli Lilly and Company (Lilly). In this conversation, Mr. Cheever requested that several pieces of information be included in the cover letter. The following paragraphs address that request.

This application is to be reviewed by the Division of Metabolism and Endocrine Drug Products as discussed during a meeting between FDA representatives and Lilly representatives on November 7, 1991.

An Investigational New Drug application for the same drug product (raloxifene hydrochloride) was submitted to the FDA (June 18, 1982) and reviewed by the Division of Oncologic and Pulmonary Drug Products under IND 20,486 as a potential treatment for metastatic breast cancer. Following the safe completion of 7 clinical

trials leading towards an indication for the treatment of breast cancer, a request was made by Lilly to inactivate the IND. This request was agreed to by the FDA on November 19, 1990.

Although new drug substance will continue to be manufactured by Lilly, new drug product for all studies to be conducted under the present IND application will be manufactured, packaged, and labeled by Applied Analytical Industries, Inc. (AAI). Their address is as follows:

Applied Analytical Laboratories, Inc.
1206 North 23rd Street
Wilmington, North Carolina 28405

Since AAI will control the final manufacture of the new drug product, the completed Chemistry, Manufacturing and Control information will be unavailable until some time after the bulk drug substance is shipped to AAI. **Since an IND number is required before the bulk drug substance can be shipped to AAI, we hereby request the assignment of an IND number based on the present submission.**

Following receipt of the IND number, Lilly will ship the bulk new drug substance to AAI for final manufacture, labeling, and assembly into clinical trial kits. Upon receipt of the appropriate information from AAI, Lilly will submit an updated Chemistry, Manufacturing and Control Information package as an amendment to the IND. For your reference the Chemistry, Manufacturing and Control Information that was included with the initial submission of IND 20,486 has been included with this submission and can be located in Section 10.A. The quality of the new drug substance and the new drug product will not differ significantly from that outlined in the initial IND (20,486) submission.

Lilly will not initiate any clinical trial with the referenced investigational drug product until it has submitted the updated Manufacturing and Control data as an IND amendment. Unless otherwise informed by the FDA, Lilly will initiate the proposed Phase 1 clinical trial 30 days (or sooner upon appropriate authorization) following the date of receipt of the amendment by the FDA.

In the previous IND application (20,486) the Lilly serial number for the drug product was designated as LY156758. That number referred to raloxifene hydrochloride. In the interim, Lilly has modified its internal procedures for the manner in which it assigns serial numbers to new chemical entities. In the current application the serial

number for the investigational new drug is denoted as LY139481•hydrochloride (HCl) where LY139481 now refers to the core molecule, raloxifene. Thus, LY156758 and LY139481•HCl both represent the same molecule, namely raloxifene hydrochloride.

The pages of the present IND application may contain multiple page numbers since all data from IND 20,486 have been included. All information from IND 20,486 which is being used to support the proposed clinical trial can be located in the appropriate IND section. Any information which is not directly pertinent to the current indication (osteoporosis) has been moved to section 10 (Additional Information). Please note that all relevant final reports from IND 20,486 which were originally included in an annual report have been moved to the appropriate IND section.

The following key may be helpful to assist the reviewers in interpreting which information is from the previous IND and which information is new. Any Arabic numeral in the upper right hand corner of a page refers to the page number from the initial IND (20,486). The page numbers for the new IND can be found in the lower right hand corner and are listed as "PAGE n".

Section 6 contains protocol H3S-LC-GCGA which will be conducted by Dr. Richard E. George in the Lilly Laboratory for Clinical Research at Wishard Memorial Hospital. The primary objective of this study is to determine the safety and tolerance of daily oral doses of up to 600 mg raloxifene given for up to 20 days prior to conducting studies in humans to specifically investigate raloxifene's effect on bone, uterus, and lipids.

Dr. George is also the monitor for this clinical trial and will be responsible for review and evaluation of information relevant to the safety of this drug. Form FDA 1572 and a curriculum vitae for Dr. George are included in Section 6(b).

Finally, please note that with this IND Lilly is initiating a new procedure for organization and assembly of IND applications. While the IND follows the guidelines established in the Form 1571 for the format and general organization of an IND application, the present application contains greater detail in the Table of Contents coupled with a larger number of corresponding tabs to assist the reviewers in locating the appropriate sections. Each volume contains a Table of Contents that is specific to that volume. Each major section is prefaced by a blue cover sheet which contains a descriptive title relating to the content of that section. We also believe that the organization of the reports in Section 8 (Pharmacology and Toxicology Data) has been

improved. We would appreciate any comments that you might have concerning these changes as we strive to improve the "reviewability" of our applications.

Please call me at (317) 276-2574 or Dr. Paul D. Gesellchen at (317) 276-4306 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

Enc.

cc: Mr. James Cheever (cover letter only)

EXHIBIT F

FDA Receipt Letter for Notice of Claimed Investigational Exemption for a New Drug

MAY [illegible] 1992

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 39,503

Date May 1, 1992

ELI LILLY AND COMPANY
Attention: M. W. Talbott, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data.

IND Number Assigned: 39,503

Sponsor: Eli Lilly and Company

Name of Drug: LY139481-HCl (raloxifene hydrochloride)

Date of Submission: April 26, 1992

Date of Receipt: April 27, 1992

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations) Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312 33)

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Dr. James Cheever at (301) 443-3520.

Sincerely yours,

Consumer Safety Officer
Division of Metabolism and Endocrine
Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-510 - yellow
HFD-510/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT G

Letter Submitting NDA Pre-Submission

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 13, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA PRESUBMISSION

Re: NDA 20-815, Evista™ (raloxifene hydrochloride)

Reference is made to a meeting (July 30, 1996) between representatives from the FDA Division of Metabolic and Endocrine Drug Products (FDA) and Eli Lilly and Company (Lilly). In this meeting Lilly proposed, and FDA accepted, the plan to presubmit Item 5 (the Nonclinical Pharmacology and Toxicology Section) of an original New Drug Application (NDA) for Evista™ (raloxifene hydrochloride). Reference is also made to a pre-NDA meeting (February 11, 1997) in which this presubmission plan was confirmed.

Lilly is herewith presubmitting Item 5 for NDA 20-815 in a total of 99 volumes.

Raloxifene hydrochloride is a new molecular entity which is an orally administered drug designed for the treatment of patients who are at risk of developing postmenopausal osteoporosis. Lilly intends to submit the remainder of the NDA for raloxifene for the indication of the prevention of osteoporosis on or about June 17, 1997.

This application is formatted and organized according to 21 CFR §314.50(d)(2) and follows the relevant sections of the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications". Lilly plans to work through the Division of Information Systems Design to coordinate the submission of a CANDA for this section of the NDA. This CANDA submission will be submitted within the next several weeks and will be an exact electronic duplicate of the paper volumes in Item 5.

We are also submitting three, 3.5 inch floppy diskettes containing tumor incidence and survival raw data from the rodent oncogenic studies (STUDIES format for toxicological data from chronic rodent bioassays). One of these diskettes is being forwarded to the pharmacology reviewer, one is being forwarded to the Biometrics Division and the third copy is being provided for archival purposes. These diskettes have been checked by Lilly systems personnel and have been verified to be free of known viruses.

Lilly understands that the initial User Fee due for NDA 20-815 will not be due until the official submission of the remainder of the NDA document in June, 1997.

To co-ordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Jennifer L. Stotka, M.D.
Director
U. S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis. IN 46285

FAX number: (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15. p.m. (EST). Any calls dealing with general issues should be made to:

Paul D. Gesellchen, Ph.D.
(317) 276-4306 (work)
(317) 578-3816 (home)
(800) 356-1643 (alphanumeric pager)

or alternatively you may reach Dr. Gesellchen via E-mail at pdg@lilly.com.

In the case of Dr. Gesellchen's absence please contact:

Jennifer L. Stotka, M.D.
(317) 276-1249 (work)
(317) 257-7606 (home)

On holidays, Saturdays, or Sundays, call Dr. Gesellchen or Dr. Stotka at home using the telephone numbers indicated.

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Paul D. Gesellchen at (317) 276-4306 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D
Director
U. S. Regulatory Affairs

Enclosures

cc: Mr. Randy Hedin (cover letter only) HFD-510
Dr. Ronald Steigerwalt (cover letter only) HFD-510
Dr. Gemma Kuijpers (cover letter only) HFD-510
Dr. Gloria Troendle (cover letter only) HFD-510
Dr. Solomon Sobel (cover letter only) HFD-510
Mr. Dan Marticello (cover letter only) HFD-715

EXHIBIT H

Receipt Letter from FDA
For NDA Pre-Submission

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-815

Eli Lilly and Company
Attention: Jennifer Stotka, M.D.
Director
Lilly Corporate Center
Indianapolis, IN 46285

MAR 17 1997

Dear Dr. Stotka:

We have received your pre-submission of the nonclinical pharmacology and toxicology section for the following:

Name of Drug Product: Evista (raloxifene hydrochloride) Tablets 60 mg

Date of Application: March 13, 1997

Date of Receipt: March 17, 1997

Our Reference Number: 20-815

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. If you have any questions regarding this information, please contact Mr. Randy Hedin, Senior Regulatory Management Officer, at 301-443-3520.

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no later than 120 days from the date of your submission.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MAR 24

EXHIBIT I

Letter Submitting NDA

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 8, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA SUBMISSION

Re: NDA 20-815--Evista™ (raloxifene hydrochloride)

This letter accompanies a submission by Eli Lilly and Company (Lilly) of an original New Drug Application (NDA) for EVISTA ™ (raloxifene hydrochloride) in 878 volumes. This submission will be supplemented by an archival copy of an identical electronic version (CANDA) of the NDA on compact disk (CD) media in Adobe Portable Document Format (PDF). Reference is made to the presubmission (March 13, 1997) of Item 5 (Nonclinical Pharmacology and Toxicology) for NDA 20-815 in 99 volumes. Reference is also made to the submission (April 2, 1997) of an electronic copy, in Adobe Portable Document Format (PDF), of Item 5. Taken together with the electronic data referred to below, these submissions constitute the complete original NDA submission for EVISTA.

EVISTA, also referred to as raloxifene hydrochloride or LY139481·HCl, is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The SERM profile of EVISTA includes estrogen agonist effects on bone and lipid metabolism, but not in uterine or breast tissues. This estrogen-like agent is a drug designed for the treatment of patients who are at risk of developing postmenopausal osteoporosis. EVISTA is to be taken orally once a day as a 60-mg tablet without regard to meals.

The primary conclusions concerning the efficacy of EVISTA are based on the 24-month interim analysis of data from 1764 randomized subjects in the three large osteoporosis prevention trials (Studies H3S-MC-GGGF, H3S-MC-GGGG, and H3S-MC-GGGH) utilizing bone mineral density as the primary efficacy endpoint.

The safety profile of EVISTA is derived from a total database of over 12,500 patients as of 16 October 1996, comprising 49 clinical studies in 27 countries. Among the 49 studies, 31 were clinical efficacy/safety studies, and 18 were clinical pharmacology studies.

Lilly believes that the NDA for EVISTA warrants an expedited review. The rationale for this conclusion is described in the Note to Reviewers that is located in this first volume [1:2.1 p16]. Certain pagination and naming conventions that are used in this NDA are also described in that section.

Lilly has met with FDA personnel on a number of occasions to discuss the development program for EVISTA since filing the IND for this drug (IND 39,503) on April 26, 1992. The interactions and agreements from those meeting are outlined in the Application Summary, H.2.1.3. Regulatory History and Agreements [2:2.1 p283] and again in the Regulatory History and Agreements section of the Background/Overview of Clinical Investigations [8:2.15 p111]. With the exception of agreements reached between the FDA and Lilly at one of these meetings, the preclinical and clinical programs were consistent with the April 1994 Draft Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmeopausal Osteoporosis.

With the exceptions noted in the summary of the FDA meeting of November 27, 1996 [2:2.1 p286], this application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the ""Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications".

All files on the CD-ROM disks of the CANDA are in Adobe PDF and can be viewed or printed by use of Adobe Acrobat Reader or Adobe Acrobat Exchange, version 2.1 or later. This CANDA represents a full, complete, and identical electronic copy of all 878 paper volumes that are being submitted as part of this application. All volume and page numbers in the CANDA match the volume and page numbers in the paper version of the NDA. Please note that the first CD-ROM disk contains a README.PDF file. This file describes the content and format of the electronic submission.

An identical review copy of the CANDA will be delivered to Mr. Ken Edmunds (FDA, Division of Information Systems Design) for installation on the FDA local area network. This installation will allow all reviewers (e.g., biopharmaceutics, biometrics, chemistry, and medical) to access the full NDA at their own private workstations. Separate arrangements have been made to instruct the lead reviewers and the senior regulatory management officer in the operation of the CANDA.

This submission is also accompanied by review and archival copies of the SAS datasets, programs, and macros (on one CD-ROM disk) that can be used to recreate the safety and efficacy analyses for the three prevention studies, GGGF, GGGG, and GGGH.

As requested (August 27, 1996, Serial No. 282) and approved by the FDA Biopharmaceutics group (December 20, 1996, Serial No. 311) this NDA submission is also accompanied by electronic media (20 UNIX-based CD-ROM disks) which contain pharmacokinetic and pharmacodynamic datasets and output files that were generated during the detailed pharmacokinetic analyses of the raloxifene data.

Finally, reference is made to triplicate 3.5 inch diskettes containing tumor incidence and survival raw data from the rodent oncogenic studies (STUDIES format for toxicological data from chronic rodent bioassays) that were submitted as part of the NDA presubmission (March 13, 1997).

All electronic media have been checked by Lilly Information Technology personnel and have been verified to be free of known viruses.

As required by the regulations, we hereby certify that the field copy is being provided simultaneously to our home FDA district office in Detroit, Michigan and that this copy contains all appropriate sections, identical to those provided to the reviewing division. Lilly affirms that all manufacturing sites listed in this application that are involved in the manufacturing, packaging, and labeling of EVISTA are available for pre-approval inspection.

The initial User Fee of $102.500.00 for this submission has been paid under User Fee number 3267. A check (#6054628) for this amount was sent to Mellon Bank on June 3, 1997 by Federal Express overnight mail. Form 3397 is provided.

A Debarment Certification has been provided.

To co-ordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Jennifer L. Stotka, M.D.
Director
U. S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 276-1652

Telephone calls should be made between the hours of 7:30 a.m. and 4:15. p.m. (EST). Any calls dealing with general issues, clinical reports, labels and literature should be made to:

Paul D. Gesellchen, Ph.D.
(317) 276-4306 (work)
(317) 578-3816 (home)
(800) 356-1643 (alphanumeric pager)

or alternatively you may reach Dr. Gesellchen via E-mail at pdg@lilly.com.

In the case of Dr. Gesellchen's absence please contact:

Jennifer L. Stotka, M.D.
(317) 276-1249 (work)
(317) 257-7606 (home)

On holidays, Saturdays, or Sundays, call Dr. Gesellchen or Dr. Stotka at home using the telephone numbers indicated.

Any calls relating to functionality of the CANDA should be made to:

Steven T. Ward
(317) 276-2952 (work)
(317) 879-8825 (home)
(317) 256-8888 (digital pager)

Any telephone calls related to manufacturing and control issues should be made to:

Gregory Davis, Ph.D.
(317) 276-4125 (work)
(317) 581-9101 (home)

or in his absence to:

Mark Slisz
(317) 276-9640 (work)
(317) 298-8782 (home)
(317) 256-5367 (digital pager)

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Finally, as provided for in the 21 §CFR 314.102(c), Lilly requests that a 90-day conference be scheduled to discuss the general progress of the review and the status of the application. It is expected that this conference will occur the first or third week in September of 1997 in order to avoid conflicts with the American Society of Bone Mineral Research national meeting in Cincinnati, Ohio (September 10-14, 1997).

Please call Dr. Paul D. Geselchen at (317) 276-4306 or me at (317) 276-1249 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U. S. Regulatory Affairs

Enclosures

cc: **Desk copies:** Cover Letter and Note to Reviewers only (Hand Delivered)

Dr. Hae-Young Ahn, HFD-870, Room 14B-18
Dr. James Bilstad, HFD-102, Room 13B-28
Dr. Sam Dutta, HFD-510, Room 14B-19
Mr. Kenneth Edmunds, HFD-070, Room 8B-45
Ms. Enid Galliers, HFD-511, Room 14B-04
Mr. Randy Hedin, HFD-510, Room 14B-04
Dr. Carolyn Jones, HFD-510, Room 14B-18
Dr. Gemma Kuijpers, HFD-510, Room 14B-04
Dr. Sheldon Markofsky, HFD-510, Room 14B-04
Mr. Daniel Marticello, HFD-715, Room 14B-31
Dr. Stephen Moore, HFD-510, Room 14B-19
Dr. Audrey Sheppard, HF-8, Room 1561
Dr. Solomon Sobel, HFD-510, Room 14B-04
Dr. Ronald Steigerwalt, HFD-510, Room 14B-04
Dr. Gloria Troendle, HFD-510, Room 14B-04

EXHIBIT J

Receipt Letter from FDA for NDA Submission

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-815

JUN 12 1997

Eli Lilly and Company
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Evista (raloxifene hydrochloride) Tablets, 60 mg.

Therapeutic Classification: Priority

Date of Application: 8 June 1997

Date of Receipt: 9 June 1997

Our Reference Number: NDA 20-815

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 8, 1997, in accordance with 21 CFR 314.101(a).

We note your request under 21 CFR 314.102(c) of the new drug regulations for an informal "90 day" conference with this Division for a brief report on the status of the review (but not on the application's ultimate approvability), and we will contact you soon with possible dates. Should you have any questions concerning this NDA, please contact Randy Hedin, R.PH.., Consumer Safety Officer, at (301) 443-3520.

JUN 26

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Enid Galliers

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

EXHIBIT K

Letter from FDA to Lilly Indicating NDA for Raloxifene Hydrochloride is Approved

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-815

Lilly Research Laboratories
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

DEC 9 1997

Dear Dr. Stotka:

Please refer to your new drug application dated June 8, 1997, received June 9, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evista (raloxifene hydrochloride) Tablets 60 mg.

We acknowledge receipt of your pre-submissions dated March 13 and April 2, and 3, 1997, and your submissions dated June 12 and 27, July 3, 10, 18, and 21, August 1, 4, 5, 11(3), 15(2), 18, 20(2), 22, 25, 28(2), and 29, September 3, 4, 9(2), 12(3), 18, 19, and 26(2), October 1(4), 2, 6, 8(2), 10, 14, 15(6), 16, 17(2), 20(2), 22, 24, and 28(2), November 3, 10, 13(4), 17(5), 19, 21, 24, and 25(2), and December 3, 5, 8, and 9, 1997. The User Fee goal date for this application is December 9, 1997.

This new drug application provides for the use of Evista Tablets for the prevention of osteoporosis in postmenopausal women.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft package insert and patient package insert labeling dated December 9, 1997, and the draft packaging labeling dated June 8, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-815. Approval of this submission by FDA is not required before the labeling is used.

DEC 12

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of the Phase 4 commitment made in your November 25, 1997, submission in which you agreed to evaluate further the genetic toxicity of raloxifene. This evaluation will include "non-standard" as well as standard tests. Please consult with our Division of Metabolic and Endocrine Drug Products, and the Center's Carcinogenicity Assessment Committee in making your determination of the appropriate studies to conduct. Also, we will be available to discuss potential technical difficulties.

Submit protocols, data, and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of this commitment in your annual report to this application. The status summary should include expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301)827-6392.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

EXHIBIT L

Description of Significant Activities Undertaken by Lilly With Respect to Raloxifene Hydrochloride during the Regulatory Review Period

EXHIBIT L

Brief Description of Significant Activities During Regulatory Review Period for Raloxifene Hydrochloride

Date	Description of Event or Activity
04/26/92	The IND submission was made.
05/27/92	The regulatory review period began.
7/1/92	The Phase I (GGGA) study began.
7/20/92	The Phase I (GGGA) study ended.
9/15/92	The Phase II (GGGB) study began.
12/18/92	The Phase II (GGGB) study ended.
3/4/93	Applicant met with the FDA to review the nonclinical data, Phase 1 and Phase 2 data, toxicology package, and pharmacokinetic data. Long-term animal efficacy plans were discussed, along with the timeline leading to submission of a NDA for raloxifene hydrochloride.
6/9/93	The Phase II (GGGC) study began.
8/6/93	Applicant met with the FDA and reviewed an efficacy study along with details for the redesigned new large animal efficacy model. The Phase 1 and Phase 2 clinical trials, including a dose-response study, were discussed along with the proposed Phase 3 pivotal protocols. Finally, the overall development timeline leading to NDA submission was presented.

9/15/93	The Phase II (GGGC) study ended.
10/15/93	Applicant and the FDA participated in a teleconference to discuss the minimum effective dose rationale, the rationale for Phase 3 dose selection, and inclusion requirements for follicle-stimulating hormone (FSH) levels.
3/7/94	The Phase 3 (GGGG) study began.
3/14/94	The Phase 3 (GGGF) study began.
3/25/94	The Phase 3 (GGGH) study began.
5/10/94	Applicant met with the FDA to review the draft of the Phase 3 pivotal protocols. As a result of this meeting, the applicant was asked to submit a detailed rationale for the enrollment estimates.
5/19/94	The rationale for enrollment estimates was submitted (Serial No. 059).
12/16/94	Applicant participated in a teleconference with the FDA and discussed details of the protocols and general requirements for NDA submission.
12/16/94	The Phase 3 (GGGK) study began.
5/3/95	Applicant participated in a teleconference with the FDA primarily to review the safety and efficacy of raloxifene hydrochloride.
7/20/95	Applicant met with the FDA to review safety and efficacy plans and to discuss adverse event data.

8/22/95	Applicant and the FDA participated in a teleconference to review particular adverse events.
9/15/95	Applicant met with the FDA to discuss the clinical pharmacology, population pharmacokinetics, and bioequivalence studies.
2/2/96	Applicant had a teleconference with the FDA Medical Reviewing Officer to discuss safety analyses of adverse events for the ongoing raloxifene hydrochloride clinical trials. Applicant agreed to send a summary document of the adverse events along with a summary of this conference call to the IND file.
2/8/96	The summary document was submitted (Serial No. 221).
4/9/96	Applicant met with the Medical Reviewing Officer to demonstrate the "draft" computer-aided new drug application (CANDA) tool.
6/6/96	Applicant met with the FDA Division chemists to review overall information and history on the Process and Chemistry, Manufacturing, and Controls (CM&C) plans.
7/30/96	Applicant met with the FDA to conduct a broad review of the raloxifene hydrochloride project.
8/27/96	IND Amendment (Serial No. 282) was submitted to the IND file requesting that certain data from

population pharmacokinetic analyses be submitted in electronic format only.

12/4/96 FDA verbally approved this request in a phone conversation.

12/20/96 Verbal approval documented in an information amendment (Serial No. 311).

11/27/96 Applicant met with the FDA to discuss the NDA format and content.

12/2/96 IND Amendment (Serial No. 308) was made in which the applicant submitted a proposed trade name for raloxifene hydrochoride with a request to have it reviewed by the Labeling and Nomenclature Committee.

12/20/96 Applicant submitted an IND Amendment (Serial No. 312) in which it provided a statistical analysis plan.

12/23/96 Applicant submitted an IND Amendment (Serial No. 313) in which it provided an update to the detailed population pharmacokinetic plan.

1/8/97 FDA confirmed in a phone conversation that the applicant's 2-year interim data dissemination plan for the pivotal prevention trials was acceptable as communicated to the FDA.

2/11/97 Applicant met with the FDA in a pre-NDA meeting. Applicant discussed efficacy and safety information from the pivotal trials and also presented submission plans for each of the

major review areas (eg, biopharmaceutics, statistics, CM&C, clinical, along with regulatory issues).

3/13/97	The NDA pre-submission was made.
06/08/97	The NDA was submitted.
12/09/97	The NDA was approved.